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A Convergent Approach to the Continuous Synthesis of Telmisartan via a Suzuki Reaction between Two Functionalized Benzimidazoles

Alex D. Martin
Virginia Commonwealth University

A CONVERGENT APPROACH TO THE CONTINUOUS SYNTHESIS OF TELMISARTAN VIA A SUZUKI REACTION BETWEEN TWO FUNCTIONALIZED BENZIMIDAZOLES

A dissertation submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy at Virginia Commonwealth University

By

Alex D. Martin

Advisor: B. Frank Gupton, Ph.D.

Professor of Chemistry, Professor and Chair of Chemical and Life Science Engineering

Virginia Commonwealth University

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Lastly, I would like to dedicate this work to the memory of my brother, Kyle.

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List of Abbreviations

ARB – angiotensin receptor blocker

RAS – renin-angiotensin system

ACE – angiotensin-converting enzyme

AT_1 – angiotensin II receptor type 1

PPARG – peroxisome proliferator-activated receptor gamma

PPA – polyphosphoric acid

TFA – trifluoroacetic acid

CDI – 1,1'-carbonyldiimidazole

HBTU – *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl) uranium hexafluorophosphate

NBS – *N*-bromosuccinimide

DCM – dichloromethane

CCl_4 – carbon tetrachloride

DMF – dimethyl formamide

MeOH – methanol

THF – tetrahydrofuran

ACN – acetonitrile

EtOAc – ethyl acetate

Et_2O – diethyl ether

ClBn – chlorobenzene

B_2pin_2 – bis (pinacolato) diboron

$PdCl_2dppf$ – [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium

KOH – potassium hydroxide

KHF_2 – potassium bifluoride

$B_2(OH)_4$ – diboronic acid

XPhos – 2- dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

PPh_3 – triphenyl phosphine

KO*t*Bu – potassium *tert*-butoxide

Pd/G – palladium nanoparticles on graphene support

NMP – N-methyl-2-pyrrolidone

DMA – dimethyl acetamide

DMSO – dimethyl sulfoxide

Abstract

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A direct and highly efficient synthesis has been developed for telmisartan, the active ingredient in the widely prescribed antihypertensive drug Micardis®. This approach brings together two functionalized benzimidazoles using a high-yielding Suzuki reaction that can be catalyzed by a homogeneous palladium source or palladium on a solid support.

The ability to perform the cross-coupling reaction was facilitated by the regio-controlled preparation of a 2-bromo-1-methylbenzimidazole precursor. The method developed is the first reported selective bromination at the 2-position of a benzimidazole and produces the first major precursor in high yield (93%). The second precursor, potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate, was prepared from commercially available 4-bromo-2-methyl-6-nitroaniline. An optimized preparation is described that provides a direct three-step process to prepare the benzimidazole and install the borate; this synthetic sequence yields the second precursor with a 90% yield and no isolated intermediates.

The two prepared precursors were combined with a third, commercially available methyl-4'-(bromomethyl)-[1,1'-biphenyl]-2-carboxylate, utilizing a short sequence of high yielding reactions to produce the telmisartan with an 83% yield from these advanced intermediates. This new convergent approach provides the active drug ingredient with an overall yield of 74% while circumventing many issues associated with the previously reported processes. Additionally, a flow-based synthesis of telmisartan was achieved with no intermediate purifications or solvent exchanges. The continuous process utilizes a tubular reactor system coupled with a plug flow cartridge, ultimately delivering telmisartan in an 86% isolated yield.

CHAPTER I

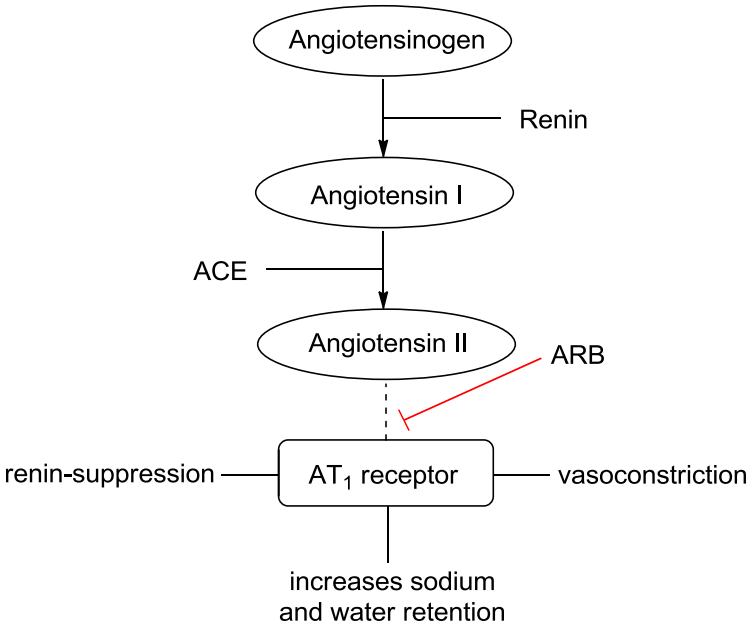
INTRODUCTION

1.1 Background and significance

In 2011, the World Health Organization reported that cardiovascular disease was the leading cause of death in the world.[1] Hypertension is a major risk factor for many cardiovascular diseases (including strokes or aneurysms) and has been implicated in 16.5% of all deaths.[2] Hypertension or high blood pressure is classified when patient's systolic and diastolic blood pressures are above 140 torr and 90 torr, respectively.[3] Over 65 million people in the United States alone are affected by hypertension.[4]

Telmisartan (**1**) is an antihypertensive drug currently marketed under the trade name Micardis.[5] This drug acts as an angiotensin receptor blocker (ARB).[6] Pharmacological agents targeting the renin-angiotensin system (RAS, Figure 1) have been explored since the 1970s.[7] The RAS begins with the cleavage of angiotensinogen by renin to form angiotensin I. From there angiotensin-converting enzyme (ACE) converts the angiotensin I into angiotensin II. Angiotensin II has a number of receptor subtypes, but the most important is the type 1 receptor (AT_1). When the AT_1 receptor is stimulated the physiological response includes increased vasoconstriction (by producing aldosterone), an increase in sodium and water retention and the suppression of renin production. The two major groups of compounds that have been used for the treatment of hypertension are ACE inhibitors and ARBs. ARBs are the preferred clinical treatment, as ACE inhibitors have been found to

cleave other peptides besides the target (angiotensin I), which can lead to many side-effects.



(image adapted from Burnier M, Brunner HR. *Lancet*. **2000**, *355*, 637-45)

Figure 1. Renin-angiotensin system

Telmisartan is the most efficacious member of the ARB drug class known as sartan drugs which includes losartan (**2**), valsartan (**3**), candesartan (**4**) olmesartan (**5**) and more (Figure 2). Telmisartan has the longest half-life (24 h), a high protein binding affinity (>99%) and a low daily dosage (40-80 mg).[8] Additionally, it has been found to have selective modulating activity of peroxisome proliferator-activated receptor gamma (PPARG).[9] This combined effect has been show to provide additional benefits against vascular and renal damage caused by cardiovascular diseases,[10] and it has been suggested that it may also prevent cognitive decline in Alzheimer's disease.[11] This high value drug has recently lost patent protection (2014) in the United States, so the development of a more efficient synthesis is timely and relevant endeavor.

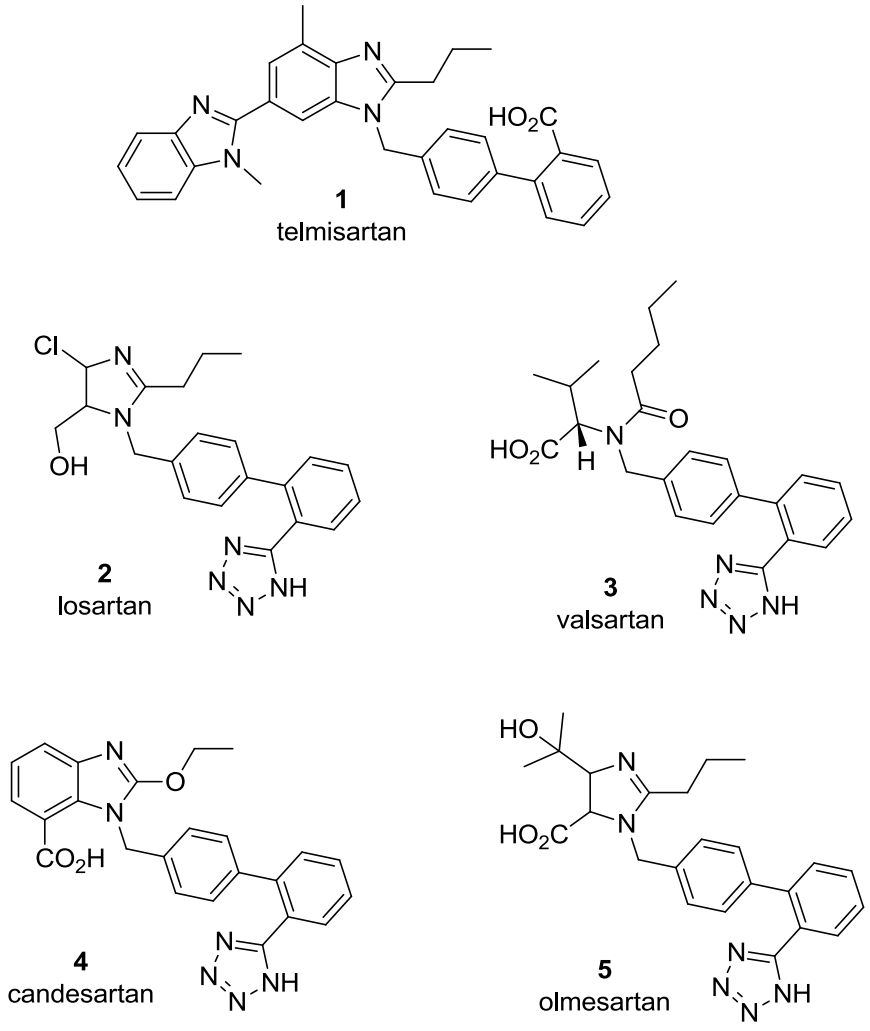


Figure 2. Selected sartan drugs

1.2 Previously reported syntheses of telmisartan

1.2.1 Ries synthesis of telmisartan (1993)

The original telmisartan process was completed by Uwe Ries et al. in 1993 (Figure 3).[12] This synthesis begins with the stepwise construction of the central benzimidazole ring from 4-amino-3-methylbenzoic acid methyl ester (**6**). To produce methyl 4-methyl-2-propylbenzimidazole-6-carboxylate (**8**), an amidation reaction with butyryl chloride is performed, followed by a nitration reaction to install the nitro group *ortho* to the newly

formed amide. The nitro group is immediately reduced using palladium on carbon under an atmosphere of hydrogen. An acid catalyzed cyclization forms the central benzimidazole component (**8**).

With the first benzimidazole (**8**) formed, the route then proceeds to form the major dibenzimidazole component. Saponification of the methyl ester of benzimidazole **8** is followed by condensation with *N*-methyl-1,2-phenylenediamine (**9**) using polyphosphoric acid (PPA) at elevated temperature (150-155 °C) to afford 1,7'-dimethyl-2'-propyl-2,5'-dibenzimidazole (**10**). The elevated temperature and acidic conditions required during this step adversely impact both product yield and purity – a major drawback of this original route that has not been adequately resolved in subsequent process improvements. Alkylation with 4'-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester (**11**) introduces the biphenyl moiety to the 1-position of the central benzimidazole ring. Trifluoroacetic acid (TFA) hydrolyzes the resulting ester to form the carboxylic acid, thus producing the final product, telmisartan (**1**). This process produces the telmisartan in a 21% yield over 8 linear steps.

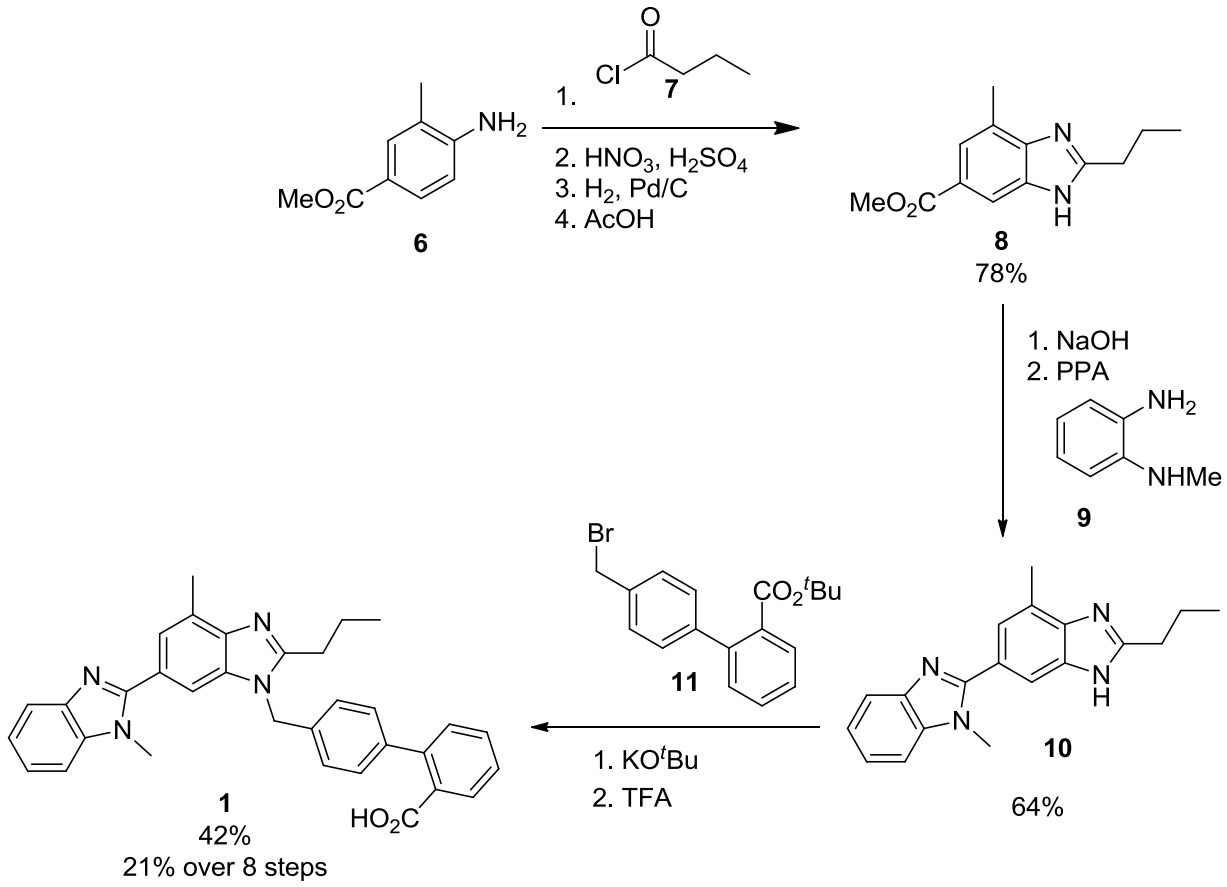


Figure 3. Ries synthesis of telmisartan

1.2.2 Reddy synthesis of telmisartan (2007)

In 2007, Reddy et al. published a process for telmisartan that utilizes the original strategy but makes a number of improvements to increase purity and yield (Figure 4).[13] Starting from a more advanced intermediate (methyl 4-butyramido-3-methyl-5-nitrobenzoate, **12**) they produce the central benzimidazole by completing a palladium catalyzed reduction of the nitro group to form the aniline which undergoes a basic catalyzed cyclization in one-pot. The use of sodium hydroxide to cyclize the ring also hydrolyzes the methyl ester producing 4-methyl-2-propyl-benzimidazole-6-carboxylic acid (**13**). The carboxylic acid of benzimidazole **13** then undergoes a condensation reaction with *N*-methyl-

phenylene diamine (**9**), again at high temperatures in the presence of PPA, to produce the dibenzimidazole (**10**). Methyl 4'-(bromomethyl)-(1,1'-biphenyl)-2-carboxylate (**14**) then undergoes a nucleophilic substitution reaction to insert the biphenyl component. The hydrochloride salt of the methyl ester of telmisartan (**15**) is isolated prior to the final hydrolysis. Finally, to produce telmisartan potassium hydroxide is used to de-esterify the methyl ester forming the carboxylic acid yielding telmisartan (**1**) with a 51% yield over 6 linear steps.

This process benefits from the availability of a more advanced starting material (**12**), reducing the number of transformations by 2. The most notable improvement from this reported method includes the use of a methyl ester (**14**) to replace the *tert*-butyl ester located on the biphenyl moiety. This replacement provides a more atom economical alternative that is also less expensive and easier to transform into the final carboxylic acid. However, this process still does not address the use of PPA at the elevated temperatures.

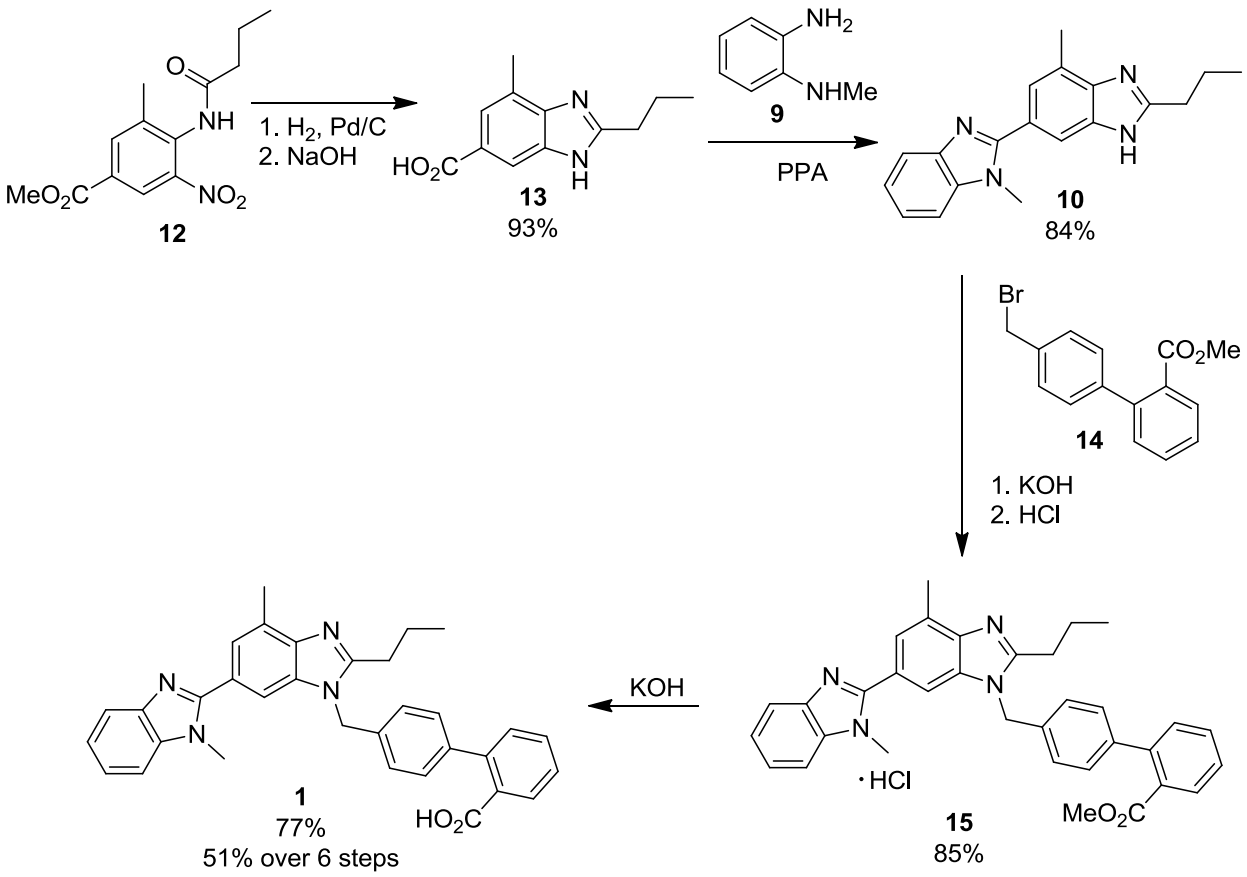


Figure 4. Reddy synthesis of telmisartan

1.2.3 Goosen synthesis of telmisartan (2008)

The year after the Reddy paper was published Goosen and Knauben reported a new process that involves a completely new approach to the assembly of the target molecule (Figure 5).[14] Beginning with an analogous starting material (3-methyl-4-nitrobenzoic acid, **16**), this process starts in a very similar fashion to the previous two syntheses. Initially, the nitro group of **16** is reduced using palladium on carbon and hydrogen. The resulting aniline is then reacted with butyryl chloride to form the amide, followed by a nitration to insert a nitro group *ortho* to the amide forming 4-butyramido-3-methyl-5-nitrobenzoic acid (**17**). In a variation from the original strategy, the carboxylic acid **17** is then coupled with *N*-methyl phenylene diamine (**9**) using 1,1'-carbonyldiimidazole (CDI), a peptide coupling reagent, to

form the outer benzimidazole ring though an *in situ* cyclization. The use of CDI forms the bond that will eventually link the two benzimidazoles, while avoiding the problematic PPA conditions. However, while the peptide coupling agents avoid the harsh conditions to form the outer benzimidazole, the cost associated is much higher making them less practical for commercial applications

Immediately following the cyclization a second palladium reduction yields *N*-(2-amino-6-methyl-4-(1-methylbenzimidazol-2-yl)phenyl)butyramide (**18**). After the formation of the outer benzimidazole, this process also introduces the biphenyl moiety in an alternative way. First, isopropyl 4'-formyl-[1,1'-biphenyl]-2-carboxylate (**22)** is prepared utilizing a decarboxylative cross-coupling reaction to couple 2-(4-chlorophenyl)-1,3-dioxolane (**21**) with potassium 2-(*iso*propoxy-carbonyl) benzoate (**20**) formed *in situ* from phthalic anhydride (**19**). With the central benzimidazole not yet formed, the biphenyl aldehyde **22** is used to introduce the biphenyl moiety and a reductive amination reaction with the amine of compound **18**.

The reductive amination forms compound **23,** with the outer benzimidazole formed and the biphenyl moiety attached, leaving the penultimate acid catalyzed cyclization to form the central benzimidazole. Finally, the saponification of the *iso*-propyl ester forms the final carboxylic acid producing telmisartan (**1**). This route provides an overall yield of 43% over 9 steps.

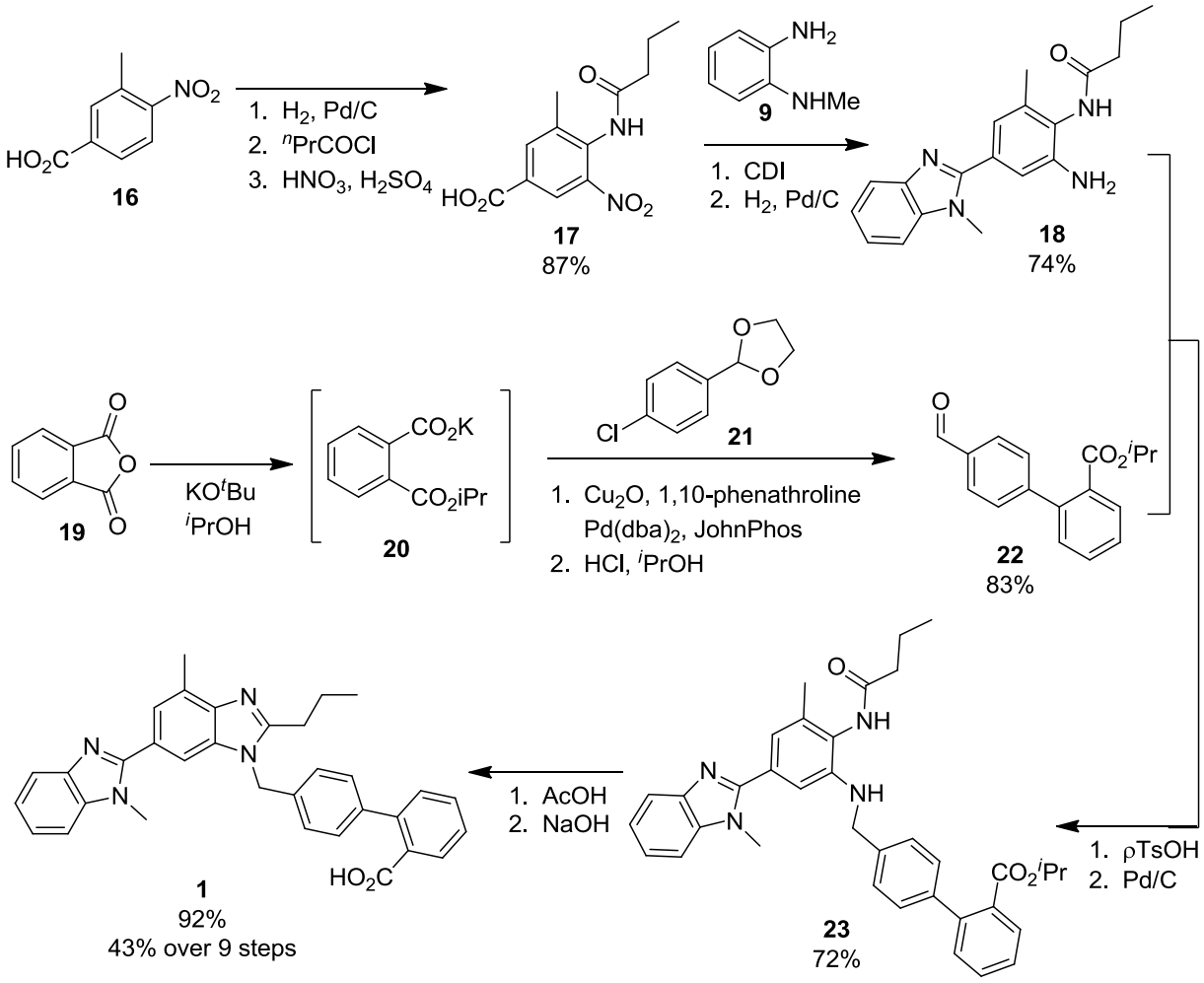


Figure 5. Goosen synthesis of telmisartan

1.2.4 Kumar syntheses of telmisartan

In a span of two years, Kumar et al. published a number of publications on the preparation of telmisartan (Figure 6).[15] The major difference introduced by this approach is the use of a 4,4-dimethyloxazoline group, instead of an ester or a nitrile, as the precursor to the final carboxylic acid.

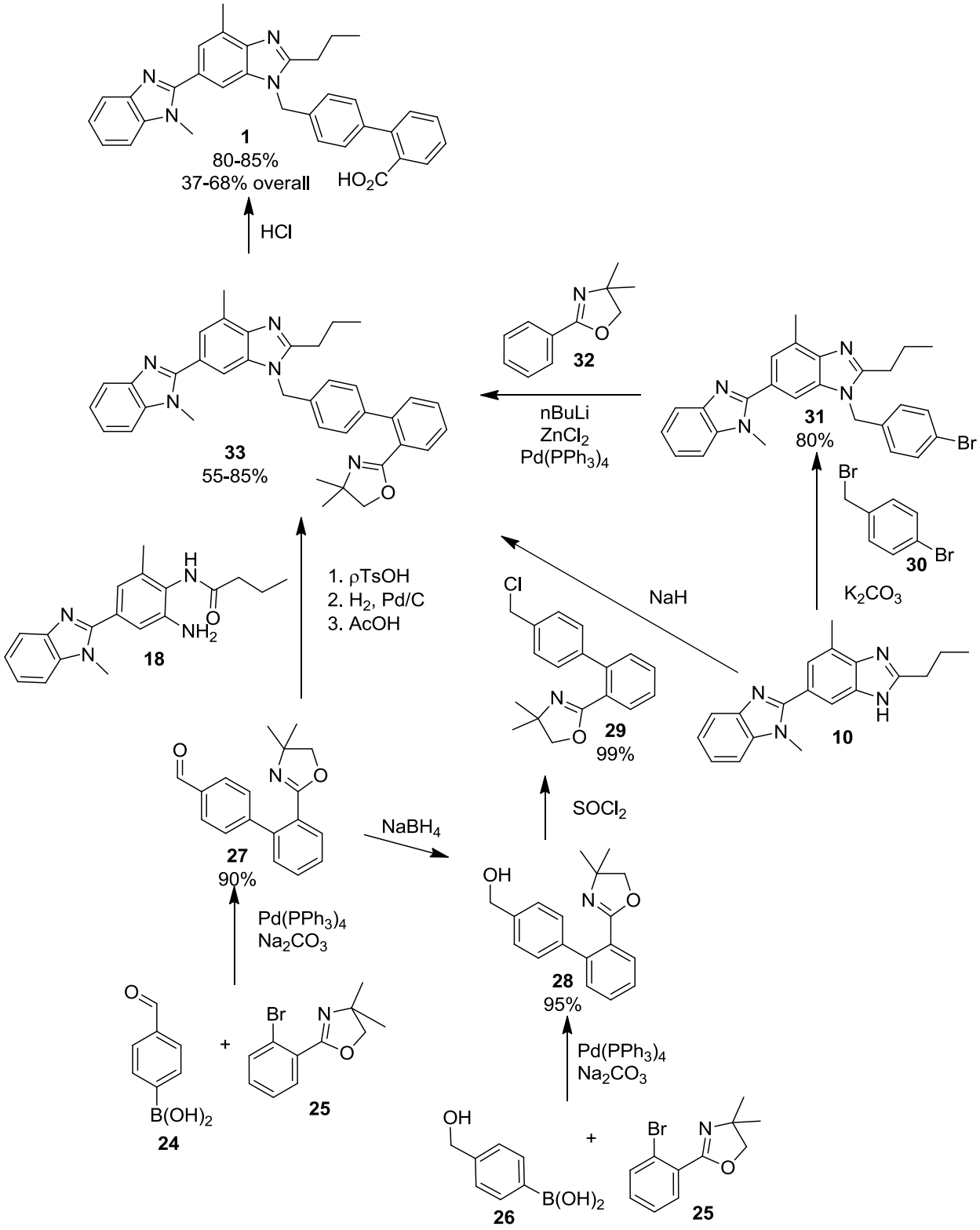


Figure 6. Synthetic routes to prepare telmisartan reported by Kumar et al. (2009-2010)

In 2009, the first telmisartan synthesis to focus on the assembly of the biphenyl moiety and the installation of the dibenzimidazole moiety was published. Starting from 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (**25**) and 4-hydroxymethylphenyl-boronic acid (**26**) a Suzuki cross-coupling reaction was used to form the biphenyl species (**28**). The alcohol was then converted to the chloride using thionyl chloride producing (4'-chloro-[1,1'-biphenyl]-2-yl)-4,4,-dimethyl-2-oxazoline (**29**) which was reacted with dibenzimidazole **10** to produce the oxazoline analogue of telmisartan **33**. The 4,4'-dimethyl-2-oxazoline was converted to the final product by refluxing in hydrochloric acid for 30 h to hydrolyze the oxazoline and form the carboxylic acid. This process produces telmisartan with a 68% over 4 steps, but failed to address the issues associated with the formation of the dibenzimidazole component of the molecule.

Later in 2009, Kumar and coworkers published a similar synthesis using a new coupling partner to form the biphenyl component. Starting with 4-formylphenyl boronic acid (**24**) and the same aryl bromide **25**, a Suzuki reaction was used to produce (4'-formyl-[1,1'-biphenyl]-2-yl)-4,4-dimethyl-2-oxazoline (**27**). The aldehyde was reduced to form the alcohol **28**, which is carried forward according to the previous synthesis producing telmisartan with a 54% yield over 5 steps.

In 2010, Kumar published another process where they utilized the same chemistry as above to produce the biphenyl aldehyde **27**. However, instead of transforming the aldehyde to the chloride and performing an alkylation, the aldehyde undergoes a reductive amination with the intermediate **18**, produced by the Goosen synthesis in 2008. After an acid catalyzed cyclization to form the oxazoline analogue of telmisartan the oxazoline is hydrolyzed according to the same hydrochloric acid reflux conditions they reported in 2009. This process produces telmisartan with a 58% yield over 4 steps but varies very little from

the Goosen approach reported in 2008 utilizing an expensive peptide coupling reagent to form the advanced intermediate **18**.

The final paper published by Kumar and coworkers, again uses the dibenzimidazole **10** as a starting material. In this iteration they perform an alkylation reaction between **10** and 1-bromo-4-bromomethyl-benzene (**30**) to produce the dibenzimidazole with a bromophenyl (**31**) instead of the biphenyl system. To form the biphenyl moiety, 4,4'-dimethyl-2-phenyl-oxazoline (**32**) is treated with *n*-butyl lithium and zinc chloride to form an organozinc compound *in situ* that undergoes a Negishi coupling with the bromide of compound **31**. This reaction produces the oxazoline of telmisartan (**33**) with only a 55%, which is a major yield hit that comes very late in the synthesis. Finally, compound **33** is carried forward to telmisartan providing a poor overall yield of 37% over three steps.

Although Kumar reports a number of different approaches that utilize some unique chemistry, they fail to address the major issues associated with preparation of telmisartan. In three of the four cases they use the dibenzimidazole **10** as a preformed starting material. In addition, much of the work completed was oriented towards the preparation of appropriate analogues of the biphenyl oxazoline; however, the oxazoline is difficult to hydrolyze requiring refluxing in hydrochloric acid for an extended period of time providing little advantage to previously established strategies.

1.2.5 Wang synthesis of telmisartan (2012)

In 2012, Wang et al. published a new synthesis of telmisartan taking a unique approach, to assemble the dibenzimidazole **10**, by focusing on using less expensive reagents and simple workups to provide a low cost production strategy (Figure 7).[16] Starting with *o*-cresol (**34**), chloroform and sodium hydroxide are used to formylate *para* to the hydroxyl group to produce 4-hydroxy-3-methylbenzaldehyde (**35**). Typically, formylation

would occur *ortho* to the hydroxyl group; however, when the *ortho* position is occupied the aldehyde is formed in the less active para position. Utilizing a similar strategy to the Goosen approach, Wang and coworkers elected to form the outer benzimidazole prior to the formation of the central benzimidazole component. This is achieved by the nitration of **35** to produce 4-hydroxy-3-methyl-5-nitrobenzaldehyde (**36**), which is followed by a methylation of the alcohol, providing 4-methoxy-3-methyl-5-nitrobenzaldehyde (**37**). To reduce the cost associated with *N*-methyl phenylene diamine used in the previous syntheses, a less expensive diamine is used, proceeding with phenylene diamine and forming the benzimidazole under oxidative conditions using hydrogen peroxide. However, the use of phenylene diamine requires methylation with dimethyl sulfate, after forming the outside benzimidazole ring, producing 2-(4-methoxy-3-methyl-5-nitrophenyl)-1-methyl-benzimidazole (**39**).

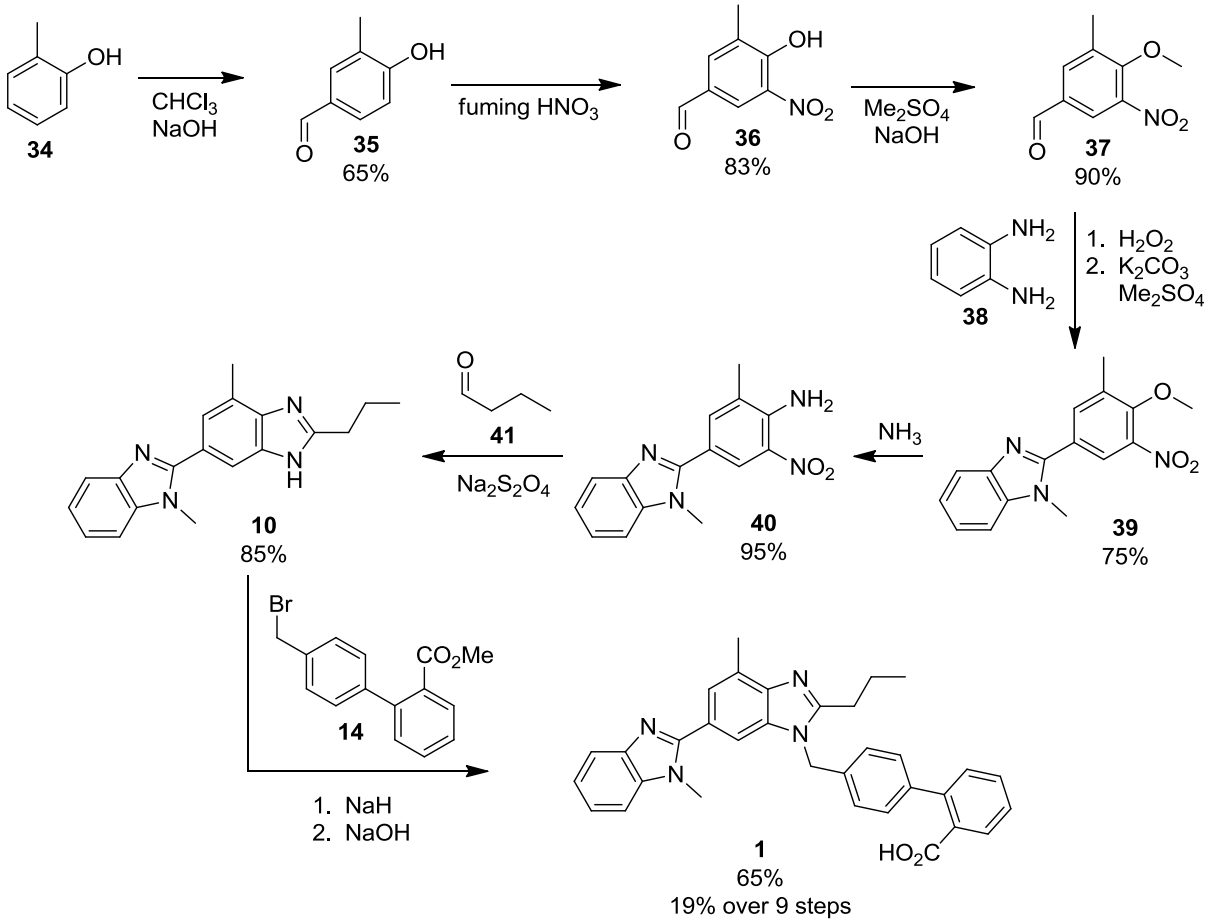


Figure 7. Wang synthesis of telmisartan

With the outside benzimidazole in place, Wang and coworkers proceeded to make the dibenzimidazole **10**. To achieve the second cyclization the methoxy group, formed early in the synthesis, is converted to an amine using ammonia to produce 2-methyl-4-(1-methyl-benzimidazol-2-yl)-6-nitroaniline (**40**). The most elegant aspect of this synthesis is the use of butyraldehyde (**41**) and sodium dithionite to form the central benzimidazole ring. This reductive cyclization uses a less expensive reducing agent, replacing the palladium catalyzed reductions used by others, to produce dibenzimidazole **10**. The approach shortens the process by eliminating the need for separate amidation, reduction and cyclization reactions, forming the benzimidazole ring in one step. The process finishes the

synthesis by then performing the alkylation using the bromide **14** and hydrolyzing the methyl ester to produce telmisartan. They report a modest overall yield of 19% over 9 steps.

1.2.6 Wen patent process for telmisartan

In 2007, Wen et al. were issued a patent for the preparation of telmisartan (Figure 8).[17] This approach starts with 4-amino-3-methylbenzoic acid methyl ester (**6**) and takes a very similar approach to assembling the dibenzimidazole, but varies from the traditional approach by performing simultaneous ring closures to form the dibenzimidazole. Wen and coworkers reported transforming that original starting material (methyl 4-amino-3-methylbnezoate, **6**) to the carboxylic acid **17** in three steps. These three steps are almost identical to the original process; however, each intermediate is isolated throughout the cyclization process. The use of butyryl chloride (**7**) forms the amide (methyl 4-butyramido-3-methylbenzoate, **42**). Compound **42** is then nitrated *ortho* to the amide using nitric acid, to produce compound **12**, followed by the saponification of the methyl ester to produce 4-butyramido-3-methyl-5-nitrobenzoic acid (**17**).

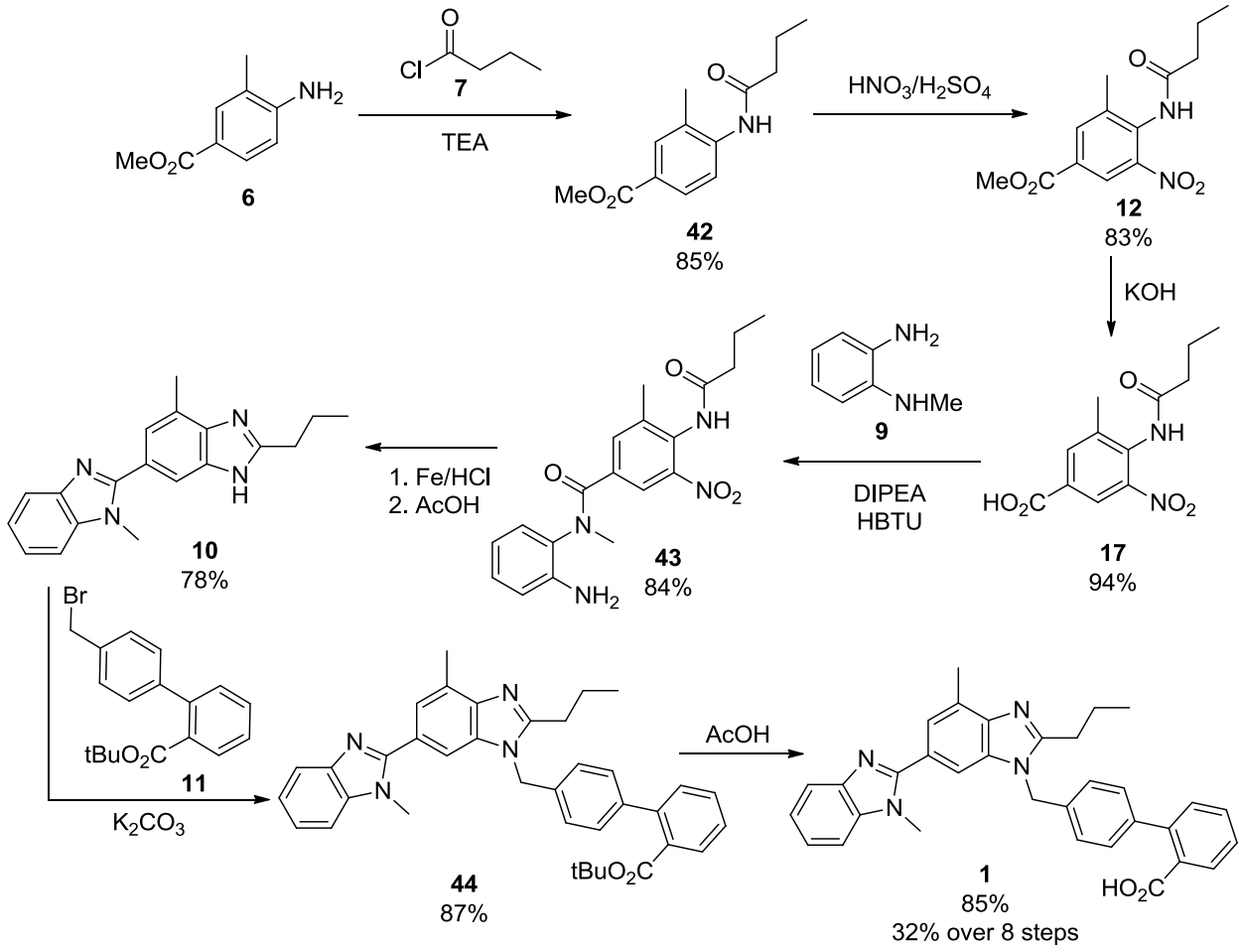


Figure 8. Wen patent synthesis of telmisartan

This is where Wen deviates from the traditional approach. Instead of closing the central benzimidazole, they use a peptide coupling reagent HBTU (N,N,N',N'-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate) to couple the carboxylic acid of **17** with *N*-methyl phenylene diamine (**9**). This produces a unique intermediate, *N*-(2-aminophenyl)-4-butyramido-*N*,3-dimethyl-5-nitrobenzamide (**43**), which features two amides with neither benzimidazole formed. The following transformation reduces the remaining nitro group to an amine, which upon reflux in acetic acid leads to both benzimidazole rings forming simultaneously to provide the dibenzimidazole **10** with a respectable yield of 78%. Following

the concurrent ring formations the biphenyl moiety is introduces as the *tert*-butyl ester (**11**) alkylating the 1-position of the central benzimidazole and is hydrolyzed using acetic acid to produce the carboxylic acid telmisartan (**1**). This process provides the final product with a 32% yield over 8 steps. Although, the simultaneous ring closures provide a novel approach to form the dibenzimidazole component (**10**) the process uses less than ideal methods to prepare the required intermediate (**43**). The use of the expensive HBTU could and the need to isolate every intermediate throughout the process can significantly increase the cost associated with this preparation of telmisartan (**1**).

1.2.7 Commercial process for preparation of telmisartan

The current commercial process starts with the major dibenzimidazole component (**10**) already formed and only includes the installation of the biphenyl moiety and subsequent formation of the carboxylic acid to produce telmisartan (**1**) (Figure 9).[18] This process uses 4'-(bromomethyl)-[1,1'-bihphenyl]-2-carbonitrile (**45**) as an alternative to the more commonly used esters. The nitrile is produced in large volumes commercially and provides a less expensive alternative while still providing a route to the carboxylic acid. Dibenzimidazole **10** is alkylated by a base mediated substitution reaction to install the biphenyl species producing the nitrile of telmisartan (**46**). The nitrile is hydrolyzed at high temperatures (150-160 °C) in ethylene glycol and is then treated with concentrated hydrochloric acid to produce telmisartan hydrochloride (**47**). After crystallization and a charcoal treatment the pH is adjusted yielding telmisartan with an 80% yield over 4 transformations.

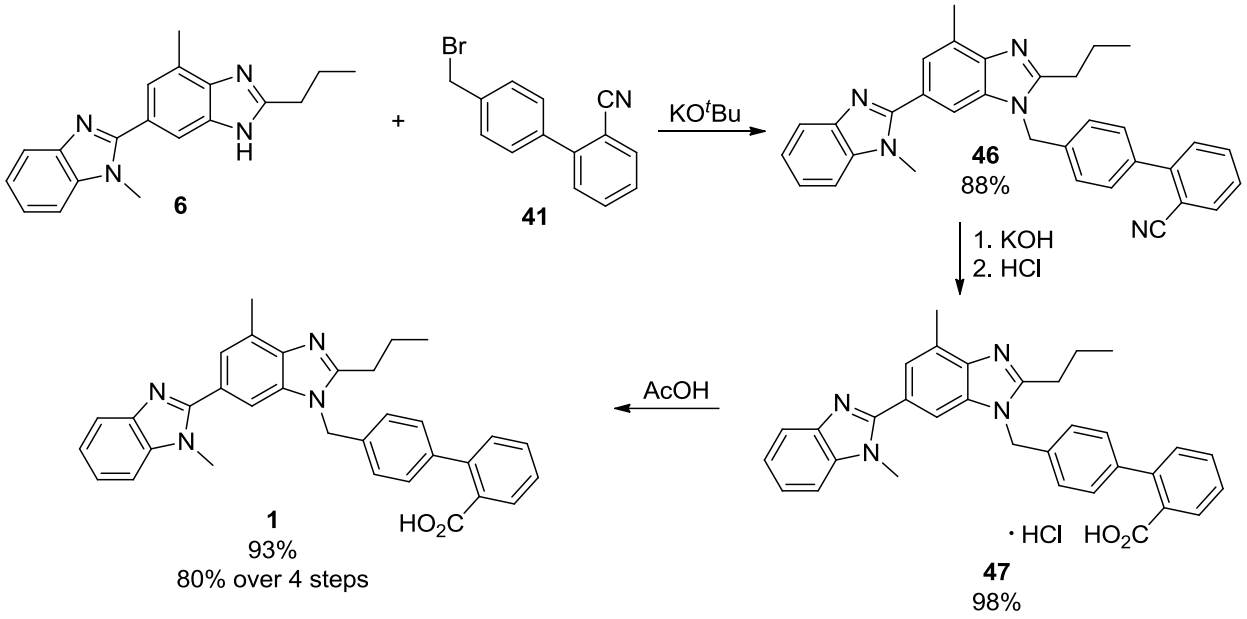


Figure 9. Commercial patent synthesis of telmisartan

1.3 Project strategy

1.3.1 Retrosynthetic analysis of telmisartan

The previously reported syntheses of telmisartan, including the current commercial process, rely on the formation of a functionalized dibenzimidazole via sequential cyclization of appropriately substituted aniline precursors. The harsh conditions associated with this very linear strategy result in significant byproduct formation resulting in lower yields. A more convergent route that overcomes these issues by exploiting chemical reactions that are both mild and selective can be envisioned. This novel synthetic strategy features breaking telmisartan into three separate synthons (Figure 10). This proposed scheme takes a completely new approach by coupling two dissimilar benzimidazole units to form the dibenzimidazole using a Suzuki cross-coupling reaction, while introducing the biphenyl moiety via a direct substitution reaction along with a functional group interconversion to produce the desired carboxylic acid derivative.

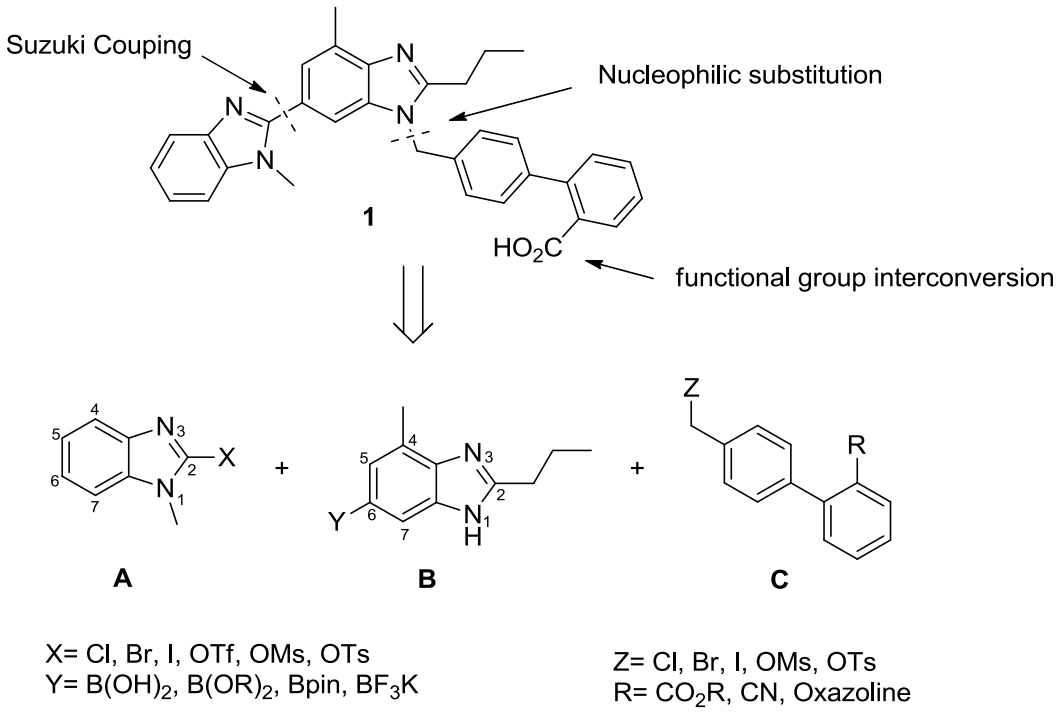


Figure 10. Retrosynthetic analysis of telmisartan

1.3.2 Recent advancements in chemical technologies

In the 20 years since the original telmisartan process, chemical technologies have greatly improved providing more efficient and economical solutions to problems in synthetic chemistry. Despite this, all of the previously reported syntheses of telmisartan still relied on the sequential formation of each benzimidazole moiety through cyclization of appropriately substituted aniline precursors. None of these routes represent a significant departure from the original synthetic strategy nor have they addressed the major shortcomings associated with the linear approach to the dibenzimidazole component of the molecule, namely the significant byproduct formation and lower yields. This new approach to the total synthesis of telmisartan is designed to improve efficiency and commercial viability while highlighting three distinct advances in chemical synthesis: the Suzuki cross-coupling reaction, solid supported catalysis, and continuous chemical processing.

In 1979, Suzuki and Miyaura reported that aryl halides could react with alkenylboranes with a palladium catalyst to form arylated E-alkenes.[19] Since that time, the Suzuki cross-coupling reaction has enjoyed broad application, ranging from the total synthesis of complex structures, to the large-scale commercial production of pharmaceuticals.[20] This Nobel Prize-winning chemistry uses mild reaction conditions that are tolerated by a wide variety of functional groups, and the inorganic byproducts can be removed easily.[21] Telmisartan is an ideal candidate to attempt a Suzuki reaction, as it features a carbon-carbon bond between two separate aryl rings.

Metal catalyzed cross-coupling reactions are generally completed under homogeneous conditions, using catalysts that are soluble in the reaction mixture. These types of reactions are great tools for creating carbon-carbon bonds and are used widely throughout the pharmaceutical industry. While homogeneous catalysis use is common, challenges still remain. The most notable disadvantages include the lack of recyclability, the need for ligands to stabilize the catalyst and the potential for contamination of the final product with toxic metals. Solid supported catalyst systems, in which the catalytic metal is deposited onto a solid support, provides a heterogeneous alternative to the use of soluble catalysts. Solid supported catalyst systems have typically shown decreased activity. Recent developments have produced new catalysts that can combine high activity and high stability while providing a recyclable catalyst that is easily separated from the product.[22] Specifically, palladium deposited on graphene sheets has been the subject of a number of recent studies.[23] The unique structure and electronic properties of graphene provide access to a solid support that is stable, active, ligand free and recyclable. [24]

Finally, we hope to use the total synthesis of telmisartan to showcase the benefits of continuous process chemistry, or flow chemistry. Flow reactors have been developed that can provide safer and more efficient chemical transformations. Small channels or tubing

provide a large surface to volume ratio[25], allowing improved heat transfer and component mixing throughout the reaction mixture.[26] This technology also provides a much easier progression for scale-up. To increase production, a single reactor could be run for a longer time or more reactors could be added in parallel.

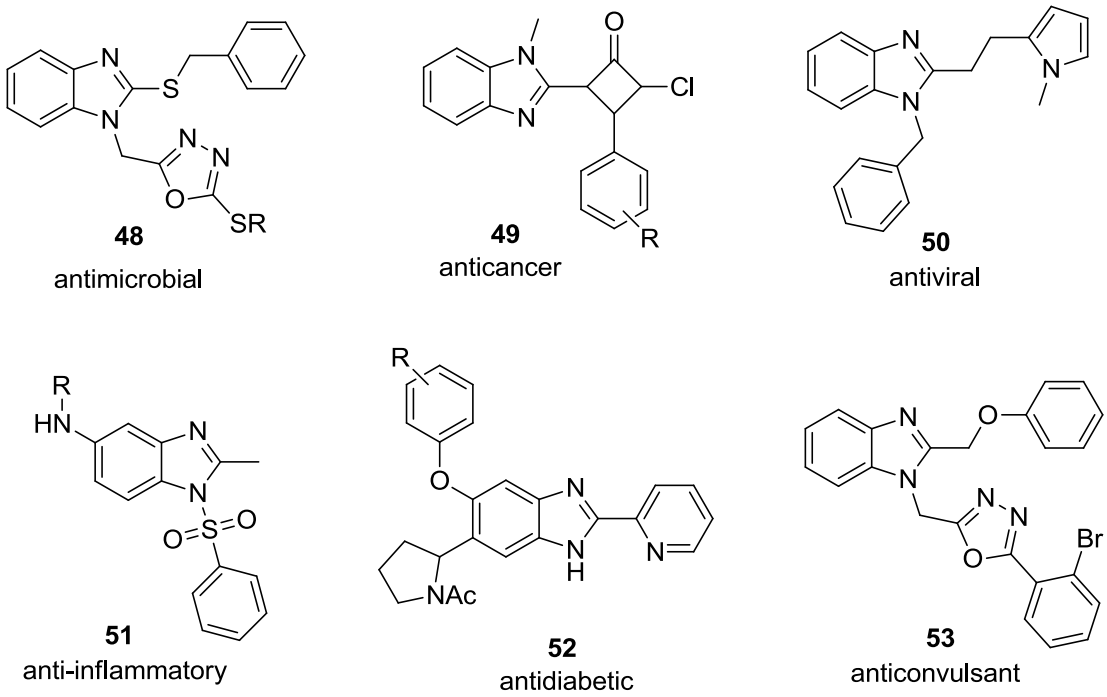
In principle, these advances in chemical technology encourage the consideration of a convergent assembly of telmisartan as opposed to the linear approach of previous syntheses. The methodology described herein will provide a more efficient assembly of the target molecule, while avoiding the problematic reaction conditions associated with the existing synthetic methods and ultimately provide a continuous chemical process to prepare telmisartan.

CHAPTER II

PREPARATION OF 2-BROMO-1-METHYLBENZIMIDAZOLE

2.1 Background

Benzimidazoles represent a promising group of potential pharmacophores.[27] Benzimidazole containing compounds have been reported to show a wide range of biological activities including: antimicrobial[28], anticancer[29], antiviral[30], anti-inflammatory[31], antidiabetic[32], anticonvulsant[33], and antihypertensive[34] (Figure 11). Most of these compounds have some functionalization at the 2-position. Therefore, finding new ways to introduce selective functionalization at the 2-position could prove to be extremely useful in further drug discovery as well as in the streamlining of current synthetic routes. With regards to telmisartan, based on the retrosynthetic analysis previously discussed, 2-bromo-1-methylbenzimidazole (**54**) was identified as a potential candidate to be used in the introduction of the outer benzimidazole component of the molecule.



(structures from Shah K et al. *Med Chem Res*. **2013**. 22, 5077-104.)

Figure 11. Pharmacologically active compounds that contain the benzimidazole moiety

There have been a number of previously reported methods for the preparation of 2-bromo-1-methylbenzimidazole (**54**). There are a significant number of drawbacks as these approaches are typically lengthy and low yielding processes. The goal of this project was to develop a selective one-step preparation of compound **54** from commercially available 1-methylbenzimidazole (**55**) (Figure 12). Inability to access this compound may provide insights into why this approach has not been previously considered.

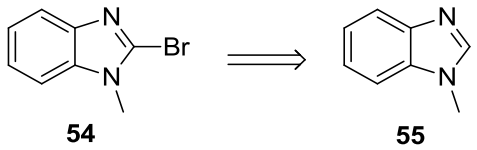


Figure 12. Retrosynthetic analysis of 2-bromo-1-methylbenzimidazole

2.2 Previously reported syntheses of 2-bromo-1-methylbenzimidazole

2.2.1 Ellingboe synthesis of 2-bromo-1-methylbenzimidazole (1992)

The first synthesis was reported in 1992 by Ellingboe et al (Figure 13).[35] They found that 4-[(methylsulfonyl)amino]benzamides and sulfonamides containing a 2-aminobenzimidazole group were the most potent as a Class III antiarrhythmic. The bromo group in the 2-position was used to substitute the 1-methylbenzimidazole onto a secondary amine attached to the benzamide/sulfonamide. Starting from 2-mercaptobenzimidazole (**56**) the thiol group is transformed to the bromide using molecular bromine and concentrated hydrobromic acid to form 2-bromobenzimidazole (**57**). Finally, to produce 2-bromo-1-methylbenzimidazole (**54**), the 1-position of benzimidazole **57** is methylated using dimethyl sulfate under basic conditions. This approach produced **54** in a 51% yield over two steps.

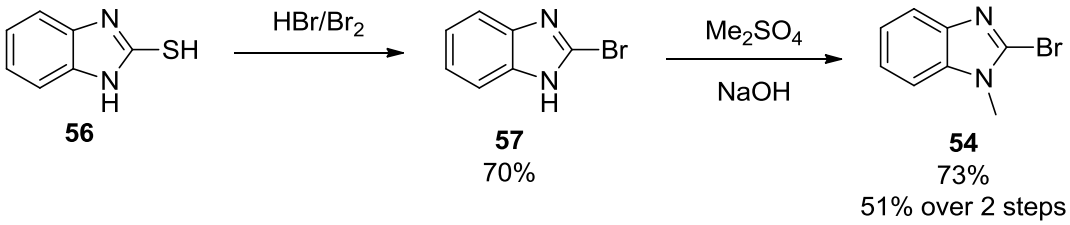


Figure 13. Ellingboe preparation of 2-bromo-1-methylbenzimidazole

2.2.2 Boga synthesis of 2-bromo-1-methylbenzimidazole (2000)

In 2000, Boga and coworkers reported a method using tetrahalogenmethanes as reagents to halogenate heterocycles using a lithium-halogen exchange (Figure 14).[36] Starting with 1-methylbenzimidazole (**55**), butyl lithium is used to selectively lithiate at the 2-position producing 2-lithio-1-methylbenzimidazole (**58**). Immediately following the lithiation

carbon tetrabromide is used to introduce a bromide into the 2-position using a metal-halogen exchange, producing 2-bromo-1-methylbenzimidazole (**54**) in a 65% yield. However, in addition to the modest yield associated with this method there is a small amount of 2-(dibromomethyl)-1-methylbenzimidazole (**59**) from the side reaction of the lithium intermediate reacting with the dibromocarbene, a byproduct from the initial metal-halogen exchange.

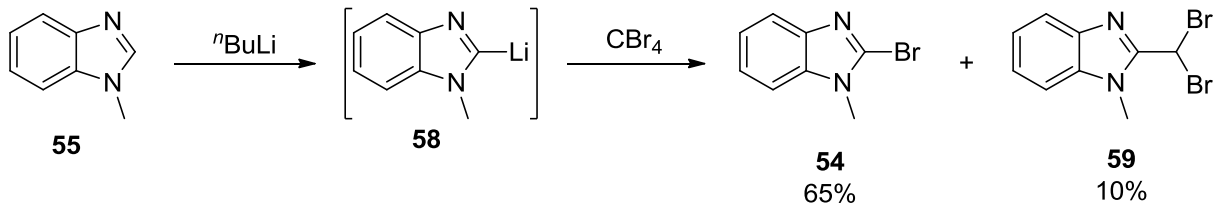


Figure 14. Boga preparation of 2-bromo-1-methylbenzimidazole

2.2.3 Costanzo synthesis of 2-bromo-1-methylbenzimidazole (2005)

More recently, Costanzo (2005)[37] reported a one-step preparation of 2-bromo-1-methylbenzimidazole (**54**) from now commercially available 2-bromobenzimidazole (**57**) (Figure 15). This method uses dimethyl sulfate to methylate the 1-position, similar to the method reported by Ellingboe. However, this process provides a more optimized conversion and increases the production of compound **54** with a moderate yield of 79%.

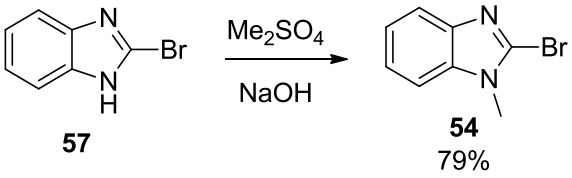
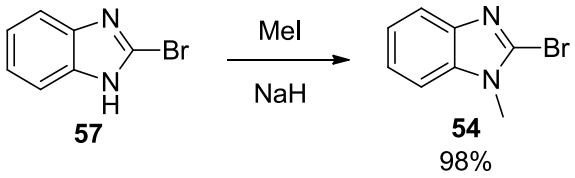


Figure 15. Costanzo preparation of 2-bromo-1-methylbenzimidazole

2.2.4 Zornik synthesis of 2-bromo-1-methylbenzimidazole (2011)

Six years later, Zornik (2011)[38] reports a high yielding process using methyl iodide and sodium hydride to perform the same methylation (Figure 16). By performing the methylation this way the yield was increased to 98% and provided an easier purification method. Although, this reaction proceeds in very high yields, methyl iodide is significantly more costly when compared to the dimethyl sulfate methods.



57 **54** 98%

Figure 16. Zornik preparation of 2-bromo-1-methylbenzimidazole

2.2.5 Verna synthesis of 2-bromo-1-methylbenzimidazole (2013)

In 2013, Verna et al. reported a preparation of 2-bromo-1-methylbenzimidazole (**54**) from o-phenylene diamine (**38**) (Figure 17). To start the diamine **38** is reacted with carbon disulfide and acetic acid to form 2-mercaptobenzimidazole (**56**). The thiol is transformed to the bromide using the method reported by Ellingboe producing compound **57**, which is then methylated using dimethyl sulfate to produce compound **54**. This three step process produces 2-bromo-1-methylbenzimidazole (**48**) in 45% overall yield.

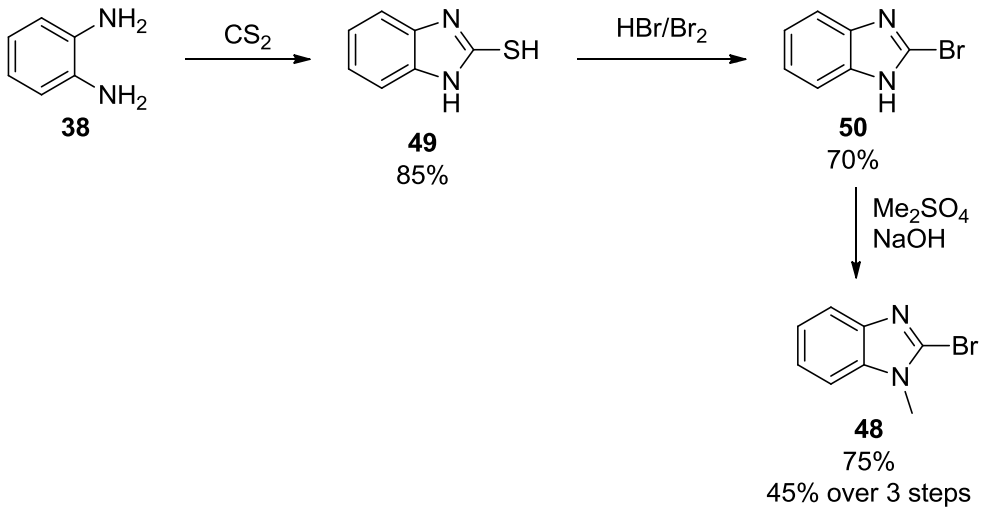


Figure 17. Verna preparation of 2-bromo-1-methylbenzimidazole.

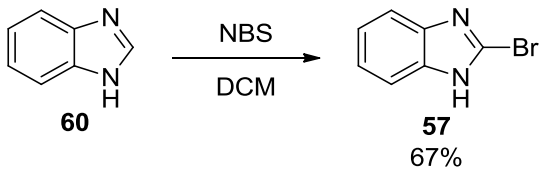
2.3 Development of a selective bromination of 1-methylbenzimidazole at the 2-position

Recently, 2-bromo-1-methylbenzimidazole (**54**) has become commercially available, but currently the cost is prohibitive towards scalable usage. The previously reported processes provide a wide variety of options to produce the desired compound, but leave room for significant improvement. The goal moving forward is to delineate reaction conditions that allow for the selective bromination of 1-methylbenzimidazole at the 2-position without the use of prefunctionalized starting materials.

2.3.1 Background on bromination of benzimidazoles

In 1996, Kawasaki briefly mentions the use of *N*-bromosuccinimide (NBS) to form the bromide at the 2-position of a benzimidazole.[39] This method provided a yield of 74%; however, specific conditions were not identified. Previously, Mistry reported a process for non-selective bromination of benzimidazole (**60**) using NBS producing **57** with a 67% yield over 1 step (Figure 18).[40] From this report it is evident that benzimidazoles are susceptible

to bromination at multiple sites. In some cases, especially in the presence of excess NBS, multiple sites can be brominated on the same molecule producing dibrominated or tribrominated species.



60 **57** 67%

Figure 18. Mistry bromination of benzimidazole

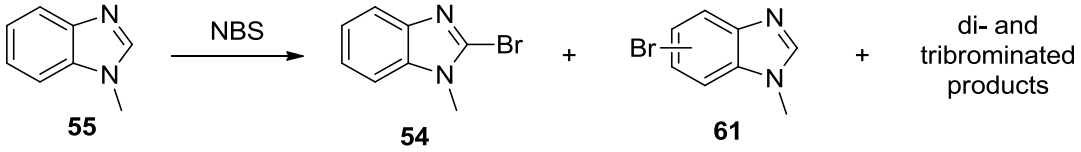
Based on the above references, brominating commercially available 1-methylbenzimidazole (**55**) using NBS was chosen as the most promising method moving forward. The goal was to achieve a commercially viable method for the selective bromination at the 2-position of 1-methylbenzimidazole in high yield.

2.3.2 Room temperature bromination studies of 1-methylbenzimidazole

A variety of commonly used solvents were selected for room temperature experiments to define selective bromination conditions. It was apparent from this initial work, that the 1-methylbenzimidazole (**55**) was susceptible to bromination at multiple sites. Depending on the solvent, the benzimidazole could be brominated at the 2, 5, 6 or any combination of positions. At room temperature a number of solvents provided the desired product (2-bromo-1-methylbenzimidazole, **54**), although the yields are very low (Table 1). Dichloromethane (DCM) and carbon tetrachloride (CCl_4) both show 37% conversion to compound **54**, but both also show a significant amount of other products (entries 1 and 4). The more polar solvents dimethyl formamide (DMF) and methanol (MeOH) showed a preference for the other brominated products with only 7% of compound **54** in DMF (entry 2)

and no desired product formed in MeOH (entry 3). Finally, tetrahydrofuran (THF) was found to produce only 11% of 2-bromo-1-methylbenzimidazole (**54**); however, despite the low conversion to desired product, no other products were seen (entry 5). This was a promising discovery and led to further exploration into improving the yield while maintain this selectivity.

Table 1. Bromination of 1-methylbenzimidazole at room temperature with 1 equivalent of NBS



55 **54** **61**

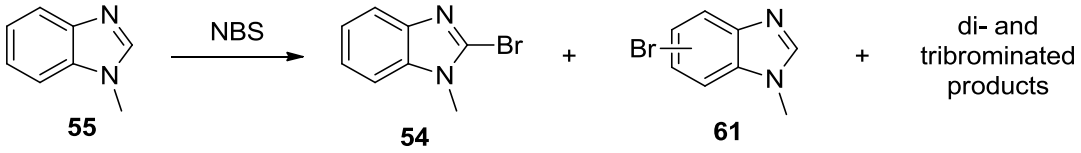
entry[a]	solvent	NBS (equiv.)	54[b]	other products[c]
1	DCM	1	37	11
2	DMF	1	7	21
3	MeOH	1	0	69
4	CCl_4	1	37	12
5	THF	1	11	0

[a] **55** (0.76 mmol), NBS (0.80 mmol), 4 mL solvent. [b] % Conversions determined by GC-MS. [c] Mixture of di-, and tribrominated byproducts.

In an attempt to increase the amount of desired product, the amount of NBS was increased from 1 to 3 molar equivalents (Table 2). In all cases the consumption of the starting material increased. Both DCM and MeOH were found to show 100% of the benzimidazole reacted; however, no desired product was produced (entries 1 and 3).

In the case of DCM, despite the appearance of the desired product with only 1 equivalent of NBS, none was found when excess brominating agent was used. It is likely that over bromination occurred and a mixture dibromo species included bromides at the 2-position. DMF shows an increase in desired product (18% up from 7% at 1 equiv.), but a similar increase to 44% was observed in other products (entry 2). In the case of THF, a low conversion of 32% was found (entry 4). However, the increase of NBS did not lead to any over-bromination as observed with the other solvents tested. This observation was a promising development while trying to provide selective bromination at the 2-position.

Table 2. Bromination of 1-methylbenzimidazole at room temperature with excess NBS



55 **54** **61**

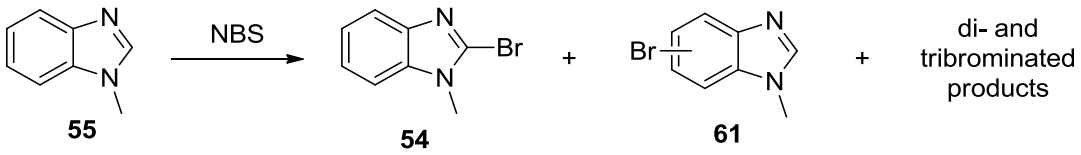
entry[a]	solvent	NBS (equiv.)	54[b]	other products[c]
1	DCM	3	0	100
2	DMF	3	18	44
3	MeOH	3	0	100
4	THF	3	32	0

[a] **55** (0.76 mmol), NBS (2.3 mmol), 4 mL solvent. [b] % Conversions determined by GC-MS. [c] Mixture of di- and tribrominated byproducts.

2.3.3 Microwave assisted bromination of 1-methylbenzimidazole

With the goal of increasing the conversion to optimum levels and maintaining the selectivity trend seen with THF a microwave-assisted solvent screen was performed and provided additional insight (Table 3). Using the higher amount of NBS, every solvent tested showed complete consumption of the starting material. This solvent screen revealed that almost every solvent tested yielded undesired mixtures of byproducts. Similar to the room temperature studies, it was found that THF provided selectivity to the 2-position and affords essentially complete conversion to the desired product (entry 8).

Table 3. Microwave assisted bromination of 1-methylbenzimidazole



55 **54** **61**

entry[a]	solvent	NBS (equiv.)	54[b]	other products[c]
1	Toluene	3	0	100
2	DMF	3	0	100
3	ACN	3	0	100
4	Diglyme	3	0	100
5	EtOAc	3	0	100
6	Et_2O	3	0	100
7	ClBn	3	0	100
8	THF	3	100	0

[a] **55** (0.76 mmol), NBS (2.3 mmol), 4 mL solvent. [b] % Conversions determined by GC-MS. [c] Mixture of di- and tribrominated byproducts.

2.3.4 Bromination of 1-methylbenzimidazole using conventional heating conditions

With the information from the microwave-assisted solvent screen, conventional heating conditions were explored to provide a more easily scalable process for the preparation of 2-bromo-1-methylbenzimidazole (**54**). By refluxing the reaction for 1 hour in THF with 3 equivalents of NBS, an isolated yield of 93% was achieved (Figure 19).

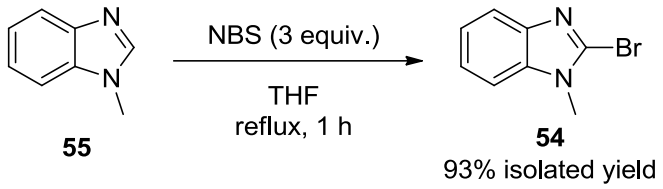


Figure 19. Selective bromination of 1-methylbenzimidazole

This is the first reported example of a selective and scalable bromination of 1-methylbenzimidazole (**51**) at the 2-position and is an essential element of the convergent strategy described earlier[41]. This selective method could find utility in the preparation of other benzimidazole adducts in the future and possibly be applied to other similar heterocycles as well.

2.3.5 Proposed mechanism for bromination of 1-methylbenzimidazole

It is unclear what provides the selectivity for the 2-position, with no over bromination. Solvents with similar polarities as THF, such as ethyl acetate (EtOAc) and chlorobenzene (ClBn), did not show the same selectivity. Similarly, other ethers tested, ethyl ether (Et_2O) and bis(2-methoxyethyl) ether (also known as diglyme), did not afford the desired product. It is possible that solvent cage effects play a role, due to the radical based mechanism for the reaction (Figure 20). The nitrogen bromide bond is cleaved (initiated by heat) producing a

free radical bromine. The bromine abstracts a hydrogen from the 2-position of the benzimidazole **51**, producing hydrobromic acid and the benzimidazole radical **58**. The hydrobromic acid then reacts with a second NBS molecule to produce molecular bromine and succinimide (**57**). The molecular bromine then reacts with the benzimidazole radical producing the desired 2-bromo-1-methylbenzimidazole (**48**) and regenerating a bromine radical to further propagate until the reaction is completed.

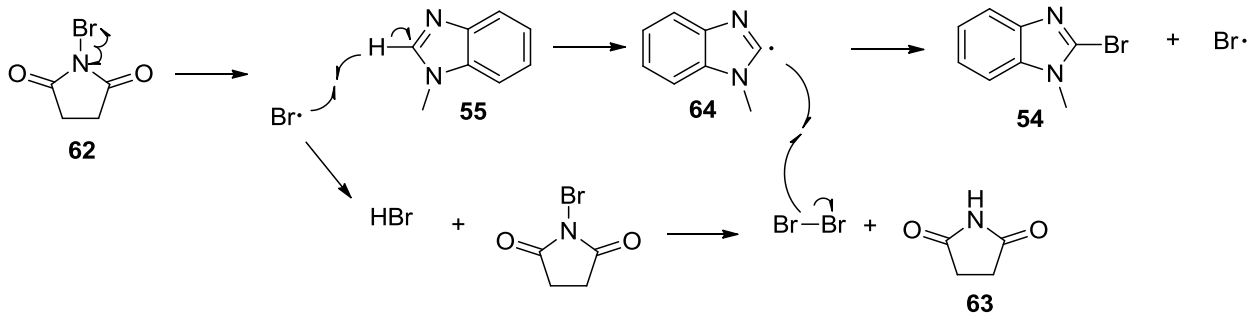


Figure 20. Proposed mechanism for bromination of 1-methylbenzimidazole using NBS

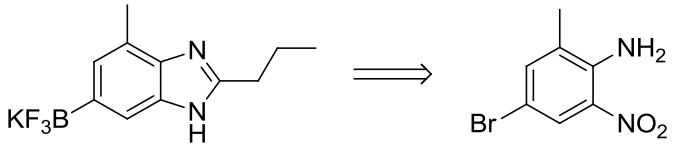
It is not known what provides this excellent selectivity; however it is hypothesized that certain physical properties of THF account for the observed reaction. NBS can act as an electrophilic bromine source in addition to the radical mechanism described earlier. It is thought that the use of NBS in other solvents can react via a different mechanism entirely or in addition to the radical mechanism. In this case, peroxides present in low levels in the THF itself can act as a radical initiator. Additional stabilization of the bromine radical can be attributed to solvent cage effects. The geometry and polarity of the five-member ring could theoretically match the imidazole portion of the benzimidazole leading to directing affects to the 2-position by physically replacing a THF molecule in the solvent cage.

CHAPTER III

PREPARATION OF POTASSIUM (4-METHYL-2-PROPYL-BENZIMIDAZOL-6-YL) TRIFLUOROBORATE

3.1 Background

With the first precursor (2-bromo-1-methylbenzimidazole, **54**) in hand, the candidate for the second precursor was identified as potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate (**65**). 4-bromo-2-methyl-6-nitroaniline (**66**) was chosen as the starting material, as it is commercially available and has the functionalization in place that can allow for a direct route to compound **65** (Figure 21). In order to prepare the benzimidazole **65** from the bromo-nitroaniline **66**, two major transformations were identified. The first step is the formation of the benzimidazole utilizing the *ortho* nitro and amino groups. Additionally, the bromo substituent provides an easy path for the installation of the required boron species, needed for the proposed Suzuki cross-coupling reaction.



65 **66**

Figure 21. Retrosynthetic analysis of potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate

3.2 Synthetic strategies for the preparation of functionalized benzimidazoles

As previously mentioned, benzimidazole structures have shown a wide-range of biological activity. A considerable amount of work has been completed, developing many different ways to synthesize derivatized benzimidazoles. This work has span over a hundred years. These routes provide several options leading to a variety of functionalized benzimidazole compounds.

3.2.1 Formation of benzimidazoles from arylene diamine and carbonyl

The most commonly reported route to benzimidazole core structures involves a condensation reaction between an arylene diamine and one of any number of carbonyl equivalents (Figure 22). This route starts with an *o*-phenylene diamine (**67**) which can react with carboxylic acids or their derivatives, such as acid chlorides, esters or anhydrides.[42] Once the condensation is completed the intermediate *o*-aminophenyl amide (**68**) is formed and can undergo an acid catalyzed cyclodehydration reaction producing the desired functionalized benzimidazole (**69**). The use of acid chlorides is much more prevalent, when compared to the other options, due to higher reactivity. The other options sometimes require harsh reaction conditions and typically limit the scope to a small set of tolerable functional groups.

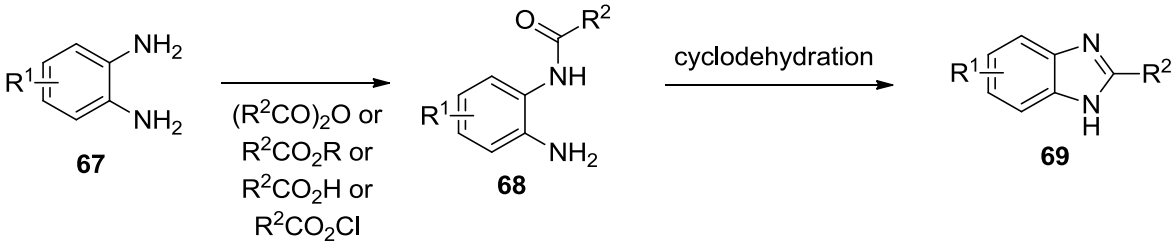


Figure 22. Preparation of benzimidazoles from arylene diamine and carbonyl

3.2.2 Formation of benzimidazoles from arylene diamine and nitriles, amides, or imidates

Arylene diamines have been found to also react with nitriles[43], amides[44] and even imidates[45] (Figure 23). These compounds, in the presence of hydrochloric acid (HCl), undergo a Pinner reaction to form *o*-aminophenyl amidines (**70**). Due to the acidic conditions, the amidine is then subsequently cyclized *in situ* releasing ammonia. This cyclization produces the functionalized benzimidazole (**69**). This strategy provides an alternative route to the more commonly used carbonyl derivatives described above.

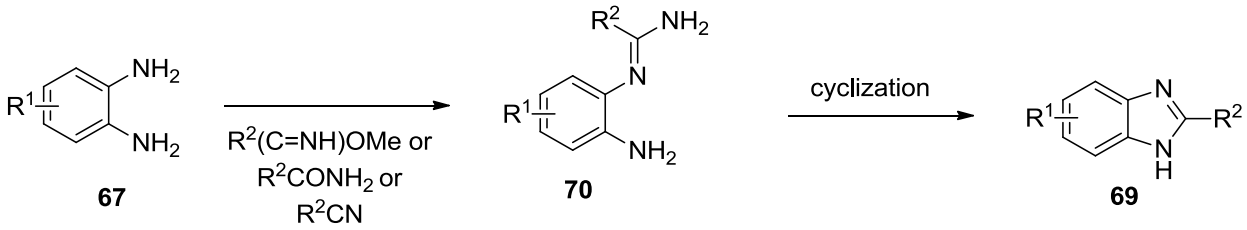


Figure 23. Preparation of benzimidazoles from arylene diamine and nitriles/amides/imidates

3.2.3 Formation of benzimidazoles from bromoanilines and amides

Much more recently, similar to the example above, *o*-bromoanilines (**71**) have been used to form analogous amidine structures (Figure 24). The amine group of the aniline (**71**) reacts with primary or secondary amides to produce an intermediate *o*-bromophenyl amidine species (**72**) via a phosphoryl chloride facilitated condensation. The final benzimidazole (**73**) is formed by a palladium catalyzed *N*-arylation providing a benzimidazole with the potential for introducing functionalization at the 1-position as well.[46]

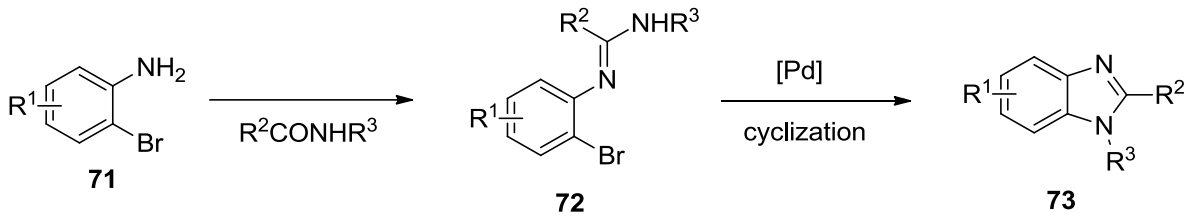


Figure 24. Preparation of benzimidazoles from bromoanilines and amides

3.2.4 Formation of benzimidazoles from aryldiamines and aldehydes

Aldehydes also have been used to produce benzimidazoles from *o*-phenylenediamines (Figure 25). When an aldehyde undergoes condensation with the diamine (**67**)[47] the benzimidazoline intermediate (**74**) is produced. This intermediate can than proceed through an oxidation and subsequent elimination to produce the benzimidazole **69**.[48] This route utilizes mild reaction conditions, such as oxone at room temperature; however, the oxidation may occur spontaneously via a disproportionation reaction leading to side products. Additionally, cases forming nonsymmetrical benzimidazoles may lead to a mixture of products. Ketones have also been reported to undergo a similar reaction,[49] but due to the need for the elimination of an alkyl group to form the final benzimidazole, this process can lead to a mixture of products when the ketone possesses dissimilar alkyl groups. This limits the feasibility of the use of ketones for many target molecules.

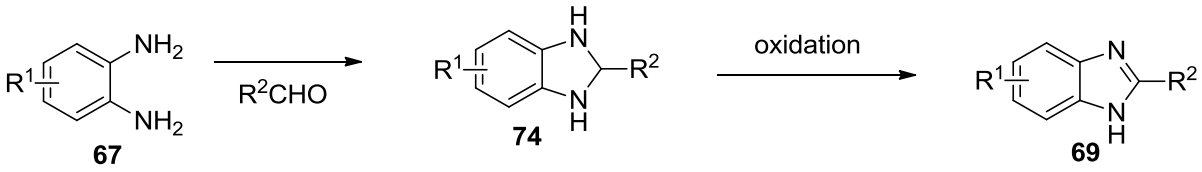


Figure 25. Preparation of benzimidazoles from arylene diamines and aldehydes

3.2.5 Formation of benzimidazoles from nitroanilines and aldehydes

The most recent approach that has been reported uses aldehydes and *o*-nitroanilines to form the benzimidazole through a benzylidene (**68**) intermediate (Figure 26). This approach completes transformation in one-step by forming the benzylidene *in situ* followed by the intramolecular reductive cyclization to form the benzimidazole **61**. This reaction has been completed using a wide range of reducing agents[50] and provides a direct one-step path from nitroaniline to the desired benzimidazole.

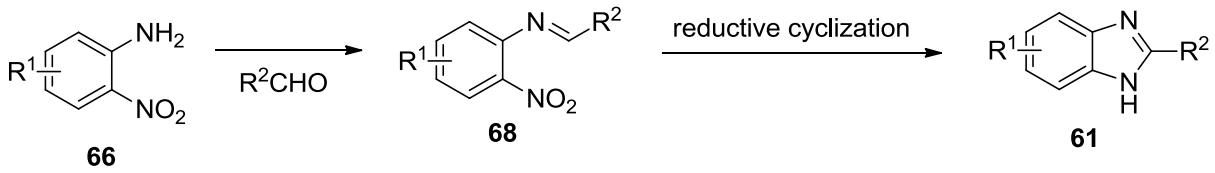


Figure 26. Preparation of benzimidazoles from arylene diamines and aldehydes

3.3 First generation process to prepare trifluoroborate (65) via three-step cyclization

In order to expedite preliminary experiments for the key Suzuki reaction, a straightforward and accessible route to the second precursor (potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate, **65**) was conceived. This route was chosen with a goal of feasibility, rather than elegance, to provide the proposed Suzuki partner rapidly. A more efficient second generation approach to this synthon was developed in parallel with the exploratory studies for the Suzuki cross-coupling reaction, with the goal of optimizing this route towards a more streamlined process.

3.3.1 Amidation of 4-bromo-2-methyl-6-nitroaniline

Initially, the cyclization was attempted first utilizing a route similar to the chemistry originally laid out by Ries and coworkers. It was proposed that the starting material (4-

bromo-2-methyl-6-nitroaniline, **66**) would undergo amidation, followed by a palladium catalyzed reduction of the nitro group and then finally cyclized to the benzimidazole under acidic conditions.

The amidation of nitroaniline **66** was completed using butyryl chloride (**7**) as the acylating reagent (Figure 27). By heating a mixture of the two compounds in ClBn for 2 hours at 100°C a good conversion was found by HPLC. In addition to the desired product **77**, a small amount of byproduct was also observed resulting from double amidation. In the presence of excess butyryl chloride the proton on the newly formed amide can be replaced by an additional amidation reaction. Conditions were found to maximize the production of **77** while limiting the amount of over amidation, providing the desired amide with an isolated yield of 82%.

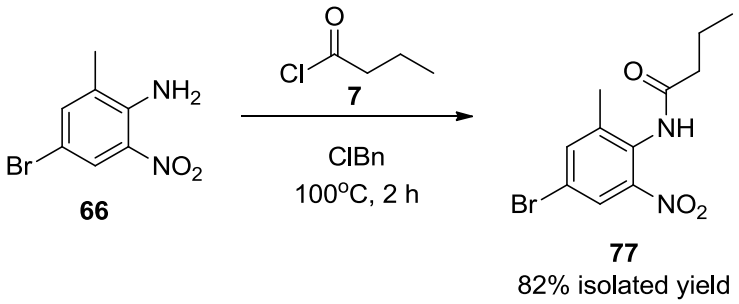


Figure 27. Amidation of 4-bromo-2-methyl-6-nitroaniline

3.3.2 Dehalogenation during palladium catalyzed hydrogenation

After the amide **77** was formed the next step was a palladium catalyzed hydrogenation reaction, intended to reduce the nitro group to facilitate cyclodehydration to the benzimidazole. The isolated *N*-(4-bromo-2-methyl-6-nitrophenyl)-butyramide (**77**) was reduced using palladium on carbon in the presence of hydrogen. However, no desired product was observed. Instead of an o-aminophenyl amide species (**78**) an unexpected

benzimidazole was formed (Figure 28). In this case, palladium catalyzed the dehalogenation of the **77**.[51] In addition to reduction of the starting material, the dehalogenation event generated hydrobromic acid which then catalyzed the cyclization of the reduced intermediate **79** to form 4-methyl-2-propylbenzimidazole (**80**).

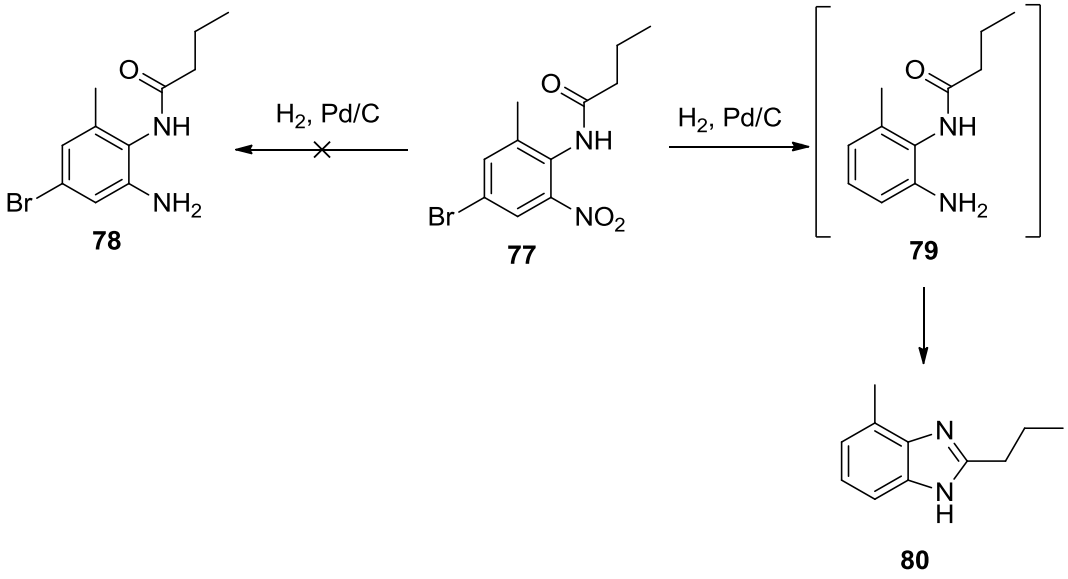


Figure 28. Dehalogenation of halide during Pd hydrogenation.

3.3.3 Palladium catalyzed installation of boronate with pinacol diboron

In order to preclude the problematic dehalogenation of compound **77**, efforts were redirected towards the installation of the boron species prior to reduction of the nitro group. Bis (pinacolato) diboron (**81**, B_2pin_2) was initially chosen as the boronating reagent due to its prevalent use throughout literature[52] and its compatibility with downstream steps. To complete this transformation a palladium catalyst was used to replace the halogen with a boron species via a similar mechanism to the Suzuki reaction.[53] However, the boronation with compound **77**, it was unsuccessful in producing the desired compound **82**. It was found

that the base required for the activation of the boronate installation leads to the cleavage of the amide bond (Figure 29).

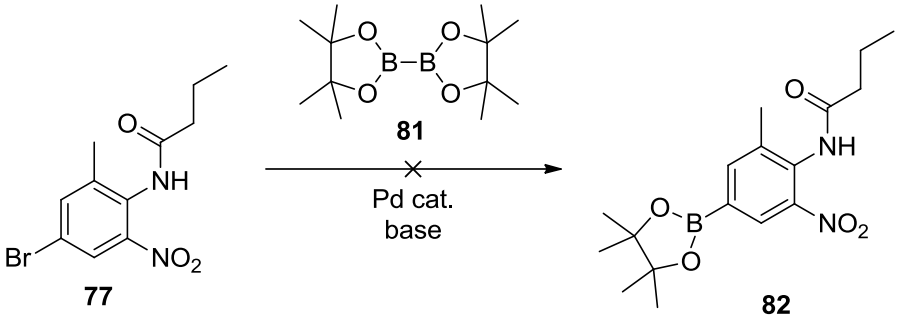


Figure 29. Unsuccessful installation of pinacol boron to amide **77**

In 2008, Velaparthi reported conditions to install the pinacol ester to 4-bromo-2-methyl-6-nitroaniline (**66**) using the diboron reagent in the presence of a palladium catalyst.[54] These conditions have the potential to be extremely effective, but also proved to be susceptible to alternative reaction pathways, as a major byproduct was observed during our preliminary experiments.

This byproduct was identified as the bianiline species (**84**) and it initially appeared to be the product of homocoupling between two molecules of the starting material (**66**). However, a more in-depth study of the reaction revealed a different mechanism for formation of the bianiline byproduct **84** (Figure 30). HPLC monitoring of the reaction mixture over time revealed formation of the desired boronic acid pinacol ester product (**83**) at early time-points. Under certain reaction conditions, both the product (**83**) and the bianiline (**76)** species were observed. As the reaction proceeded the decrease in the observed quantity of boronic ester (**83**) could be correlated to an increase in the bianiline byproduct (**84**). These observations led to the conclusion that the bianiline is most likely not the artifact of a direct homocoupling between two molecules of the starting bromoaniline (**66**). Rather, the

unwanted byproduct is likely caused by a Suzuki reaction between the desired product (**83**) and an unreacted bromoaniline (**66**), catalyzed by the palladium catalyst required for the installation of the pinacol boron ester.

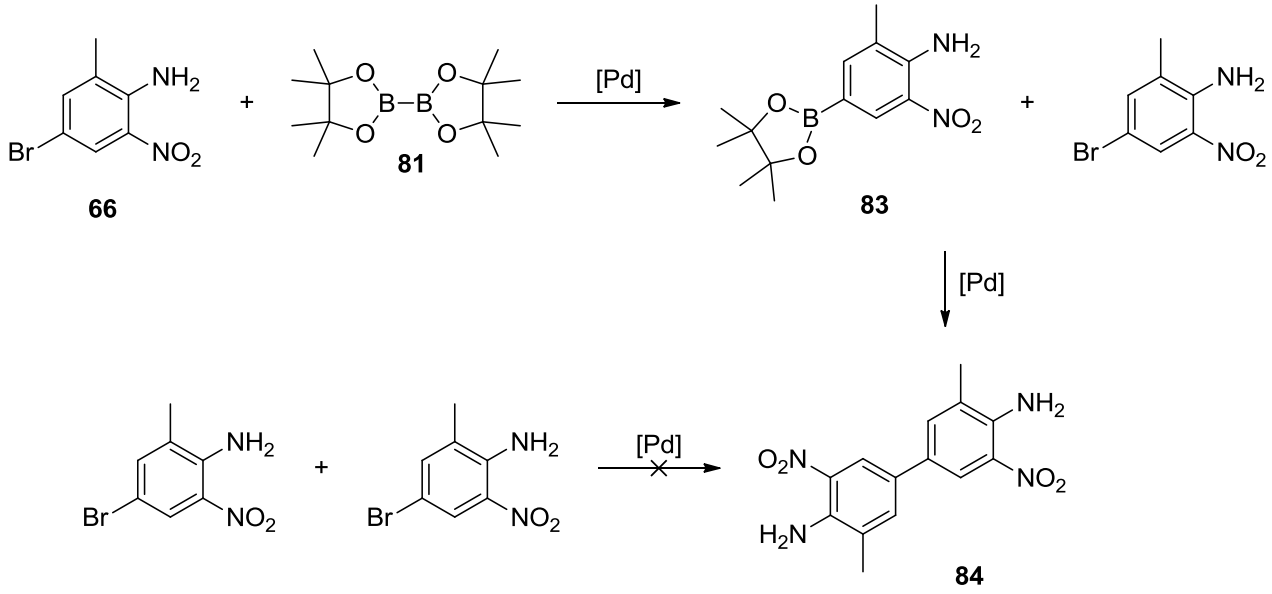


Figure 30. Proposed route to bianiline byproduct **84**.

*3.3.4 Optimization studies for installation of pinacol boron to nitroaniline **66***

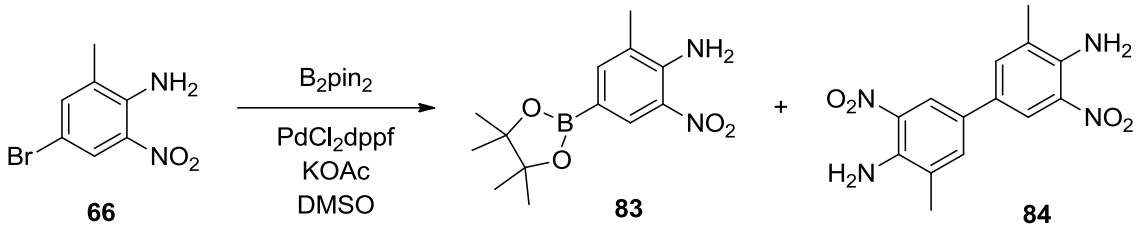
In an attempt to find conditions to minimize the amount of bianiline byproduct (**84**) being formed a set of reactions were screened in order to gain a better understanding of how specific process parameters contribute to byproduct formation (Table 4). The three factors studied were catalyst loading, equivalents of diboron reagent and reaction concentration. The reaction of 4-bromo-2-methyl-6-nitroaniline (**66**) and pinacol diboron (**81**) was run in the presence of only 2 mol% of the catalyst, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium ($PdCl_2dppf$) and only a slight excess of diboron.

These conditions resulted in low conversion to the desired product (24%, entry 1) and produced a similar amount of byproduct (25%) while the remaining starting material remained unreacted. An increase in catalyst loading (entry 2), led to complete consumption of the starting material and increased the yield of **83** up to 63%, but also increased the amount of bianiline **84** to 37%. Alternatively, by increasing the amount of diboron to 5 equivalents (entry 6) a significant improvement was noticed. The large excess of the boronating reagent produced a much higher conversion of 74% with only 8% of the bianiline byproduct (**84**) formed.

Finally, optimal conditions were found by running the reaction in a more concentrated solution (entries 8 and 9). Using the higher amounts of the palladium catalyst and the pinacol diboron reagent, the higher reaction concentration led to complete conversion to the desired (4-amino-3-methyl-5-nitrophenyl) pinacol boron (**83**) with no byproduct observed.

Table 4. Effects of process parameters on boronation of

4-bromo-2-methyl-6-nitroaniline



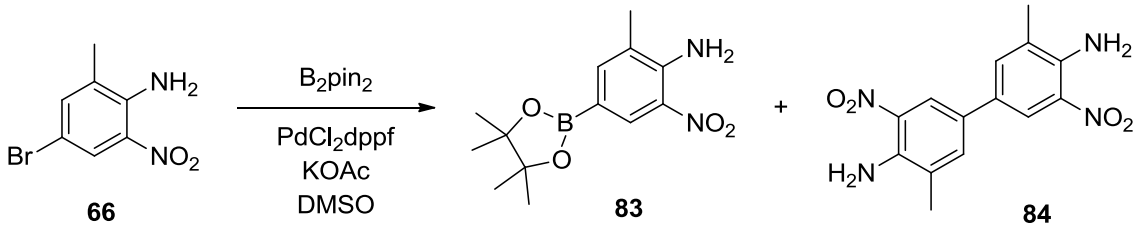
entry[a]	B_2pin_2 (equiv.)	DMSO (mL)	Pd (mol%)	83[b]	84[b]
1	1.05	4	2	24	25
2	1.05	4	10	63	37
3	1.05	1	2	74	26
4	1.05	1	10	81	19
5	2.5	2	5	93	7
6	5	4	2	74	8
7	5	4	10	95	5
8	5	1	2	97	3
9	5	1	10	100	0

[a] **77** (0.43 mmol), KOAc (1.3 mmol), under nitrogen at 100°C for 5 h. [b] Conversions determined by HPLC

Although this first screen provided reaction conditions that avoided byproduct formation, the high cost of both the palladium catalyst and the pinacol diboron reagent resulted in concerns about the cost impact of this reaction. With the intermediate reaction

conditions (Table 4, entry 5), which lowers catalyst, diboron, and reaction concentration each by half, a reasonable conversion of 93% could be achieved. With that in mind a secondary screen was aimed at optimizing conversion while taking into account the cost associated with the components (Table 5). It was found that the reactions with highest concentration provided excellent conversion with minimal by product. Reactions with only 2 equivalents of B_2pin_2, ranging from 2 mol% catalyst up to 10 mol%, all showed conversions above 90%.

Table 5. Effects of catalyst loading on boronation of 4-bromo-2-methyl-6-nitroaniline.



66 **83** **84**

entry	B_2pin_2 (equiv.)	DMSO (mL)	Pd (mol%)	83	84
1[c]	2	1	2	96	4
2	2	1	5	97	3
3	2	1	10	98	2

[a] **77** (0.43 mmol), KOAc (1.3 mmol), under nitrogen at 100°C for 5 h. [b] Conversions determined by HPLC

The reaction of 4-bromo-2-methyl-5-nitroaniline (**66**) and pinacol diboron (**81,** 2 equiv.) in the presence of $PdCl_2$dppf (5 mol%) led to the formation of the desired (4-amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (**83**) with an isolated yield of 95% (Figure 31).

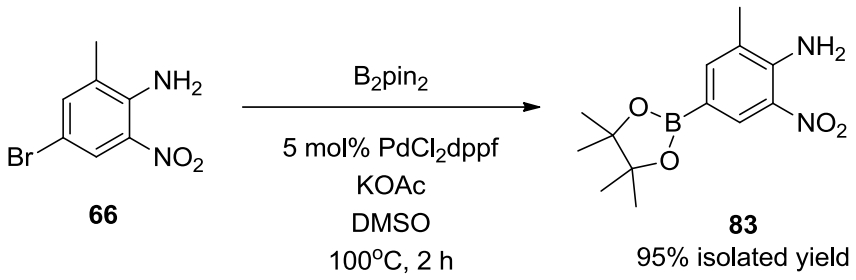


Figure 31. Pinacol boron installation to form **83**.

3.3.5 Formation of benzimidazole via three-step cyclization

With the installation of the boron complete, nitroaniline **83** was successfully converted to the benzimidazole without concern for cleavage at the 6-position. This overall transformation was carried out through a series of non-isolated intermediates (Figure 32), constituting a slight modification to the original process developed by Ries.[12] Starting with (4-amino-3-methyl-5-nitrophenyl) boron acid pinacol ester (**83**) a slight excess of butyryl chloride (**7**) is added. When heated in chlorobenzene the reaction forms the corresponding amide (**85**). After a solvent exchange to methanol, palladium on activated carbon is introduced to solution and then the reaction is stirred under an atmosphere of hydrogen. This leads to the catalytic hydrogenation of the nitro group to produce the *o*-aminophenyl amide (**86**). Then after refluxing in acetic acid to facilitate the cyclodehydration, 4-methyl-2-propylbenzimidazol-6-yl boronic acid pinacol ester (**87**) is isolated with a 63% yield over the three steps. It was observed that some cyclization can occur without the AcOH reflux step. It is likely due to the HCl formed during the amidation step. However, the AcOH is required to achieve a higher yield, assisted by the elevated temperature.

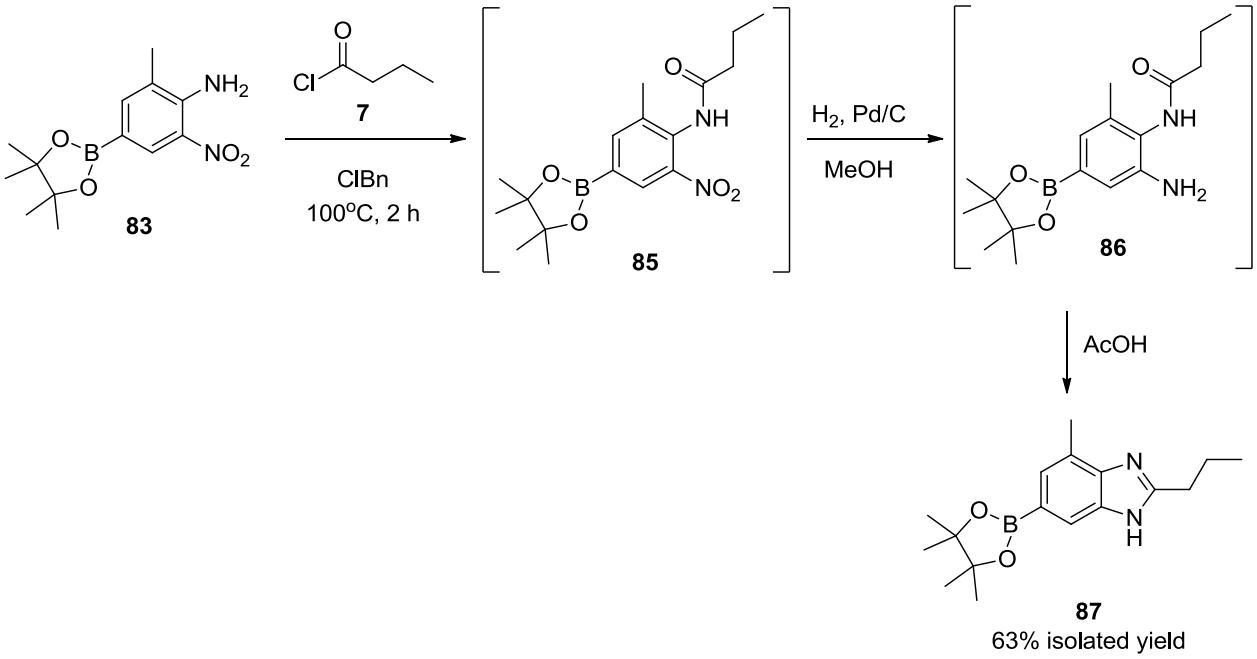


Figure 32. Three-step cyclization to form benzimidazole **87**.

*3.3.6 Formation of potassium trifluoroborate salt **65***

With the benzimidazole formed and a boron species installed one final transformation is needed to convert synthetic intermediate **87** into a trifluoroborate salt, the desired synthon for the proposed convergent approach to telmisartan. Trifluoroborates have been shown to have a wide range of benefits over more traditional boronic acid derivatives.[55] For example trifluoroborates are typically easy to purify out of solution. Most trifluoroborates have very limited solubility in aqueous systems and most organic solvents, and can therefore often be precipitated out of the reaction mixture. They are also highly stable compounds being able to tolerate the presence of air and water while being stored. Finally, and most importantly, trifluoroborates have been found to be more reactive towards Suzuki cross-coupling reactions as compared to other boron species. This is likely due to the fact that trifluoroborates already have a quaternary boron, which is activated to undergo the transmetallation step in the catalytic cycle of the Suzuki reaction.

To form a trifluoroborate from a pinacol ester, potassium bifluoride (KHF_2) is used, and it tends to react quickly and give very high yields.[56] In this case, the pinacol ester of benzimidazole **87** was found to show complete conversion to the trifluoroborate **65**. As aqueous KHF_2 is added to the benzimidazole **87** in a THF solution the reaction would proceed in an unusual THF/water biphasic system. After stirring at room temperature the product is easily purified by removing the THF and filtering the precipitate that is formed.

In order to maximize the amount of product being formed and streamline the process, formation of the desired trifluoroborate salt (**65**) was telescoped with the previous synthetic sequence. When all five steps, starting from the nitroaniline (**66**) ,are completed without any isolation, the final Suzuki partner (**65**) can be produced and easily isolated in pure form. This method provides potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate in five steps with an isolated yield of 60% (Figure 33).

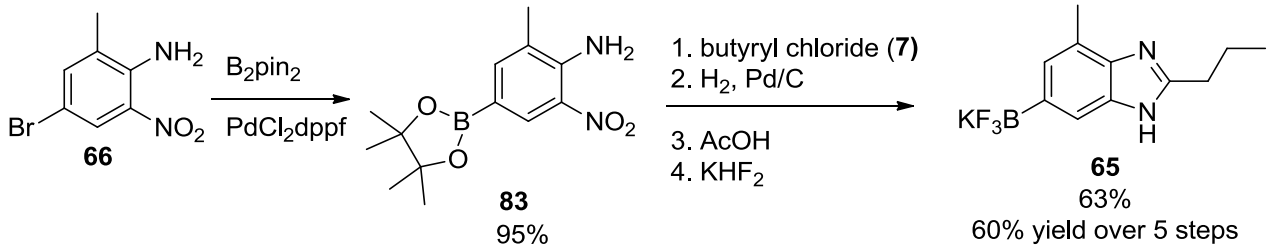


Figure 33. Five-step formation of trifluoroborate **65** nitroaniline **66**

3.3.7 Formation of potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate

An alternative approach was also explored and experiments were performed converting the pinacol boron of the nitroaniline **83** to the trifluoroborate (**88**) (Figure 34). This transition occurred with good conversion producing the desired potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate (**88**) with a 93% isolated yield. However, attempts to carry the nitroaniline **88** forward to the benzimidazole proved to be unsuccessful. The

significant solubility issues proved problematic and in some cases it appeared the boron-carbon bond was cleaved during cyclization attempts.

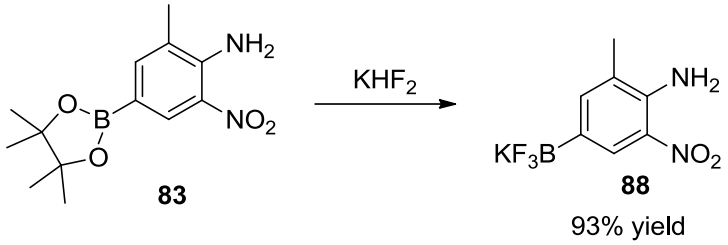


Figure 34. Formation of potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate

3.4 Second generation process to prepare trifluoroborate (65) via reductive cyclization

Although the first generation route to the trifluoroborate salt **65** offers a number of advantages over previously published routes to constructing the central benzimidazole moiety of telmisartan, there was room for significant improvement of this fragment. In order to establish the proof of concept for a Suzuki based approach to the dibenzimidazole core of telmisartan, gaining immediate access to the key synthons was of great importance. Accordingly, the first generation route to the trifluoroborate salt **65** was devised to be expeditious, but there are multiple factors that would become major deterrents to applying this chemistry on an industrial scale.

There were a few major areas that were targeted for improvement from the first generation process. First, both the installation of the boron species and the reduction of the nitro group require a rather large amount of palladium catalyst, which can be expensive. By finding alternate transformations the use of palladium could be significantly reduced or potentially eliminated completely. The other issue involves the selection of pinacol diboron (**81**) to introduce the boron species. This synthetic approach greatly improves the atom

economy of the process. The large pinacol ester is added and subsequently discarded upon transformation into the trifluoroborate. Moreover, the need to use a large excess (2-5 equivalents) during this step contributes to a significant amount of additional waste.

*3.4.1 Reductive cyclization of nitroaniline **83** with butyraldehyde*

The first item addressed was the problematic and moderate yielding synthetic sequenced used to from the benzimidazole component. An alternative route was explored and provided a more efficient approach to the preparation of the potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate (**65**). Aldehydes have been shown to react with *o*-nitroaniline species, in the presence of sodium dithionite, to form benzimidazole rings directly via a reductive cyclization. The reductive cyclization route was explored and butyraldehyde (**41**), a less expensive and safer carbonyl compound was used instead of butyryl chloride (**7**), which was used in the first generation process. Butyraldehyde (**41**) avoids the acylation used previously and is installed via a reductive amination. Secondly, the expensive palladium on carbon can be replaced by sodium dithionite. Sodium dithionite is a relatively inexpensive reagent that has been shown to reduce aryl nitro groups to amines while tolerating a large range of other functional groups.[57]

The reductive cyclization was initially performed starting from (4-amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (**83**). Refluxing this nitroaniline in a 50% methanol/water mixture and with a large excess of sodium dithionite produced the benzimidazole **87**. In a similar fashion to the first generation process, the pinacol boron was not isolated, but instead transformed directly to the trifluoroborate to ease purification and increase amount of product recovered.

This initial process yielded the desired synthon, potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate (**65**), with a moderate isolated yield of 60% over two

steps (Figure 35). Although the yield for this process is very similar to the first generation process, significant improvements have been realized. Specifically, the removal of one palladium catalyzed step and the elimination of two unit operations. This two-step process achieved the same transformation that previously required four chemical steps. However, the moderate yield still left a significant amount of room for improvement.

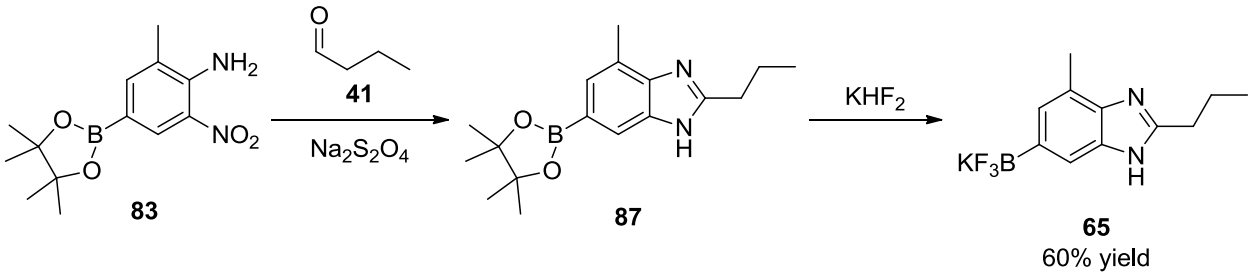
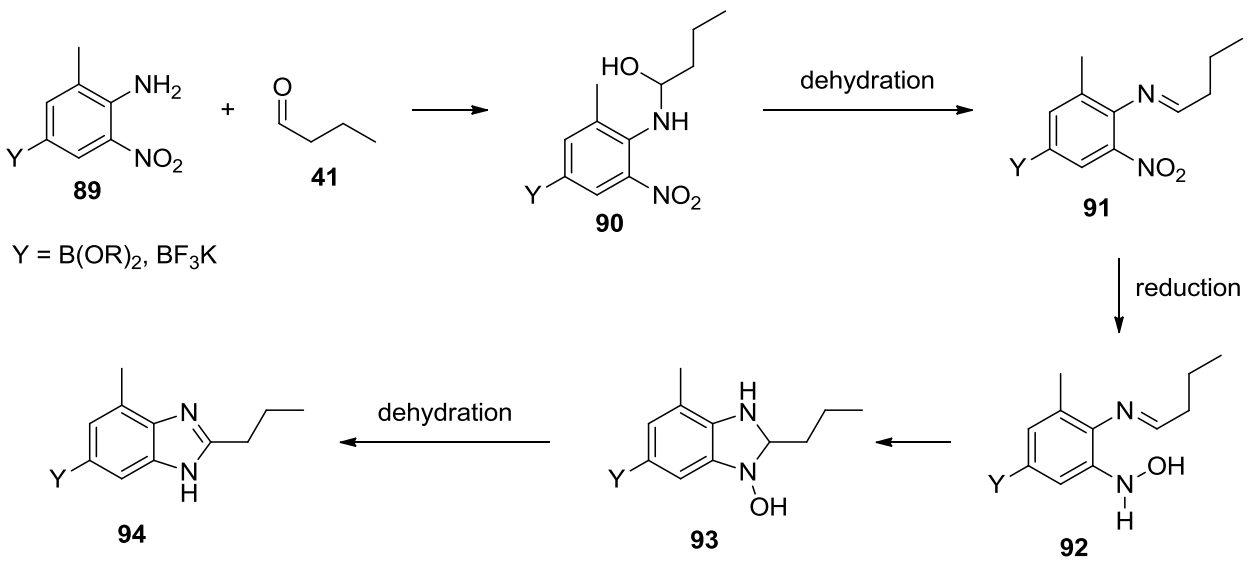


Figure 35. Two-step preparation of trifluoroborate **69** from nitroaniline pinacol boron

3.4.2 Proposed route to form benzimidazoles via reductive cyclization

Although, sodium dithionite is capable of reducing nitro groups all the way to amines, in the case of *o*-nitroaniline substrates that have been exposed to aldehyde reagents, a reductive cyclization pathway takes precedence (Figure 36). The process starts by the amino group of the nitroaniline (**89**) condensing with aldehyde **41** to the o-nitrophenyl imine **91** through the hemiaminal **90**. The nitro group of the newly formed imine **91** is then partially reduced to the hydroxylamine **92**. The hydroxylamine is poised to attack the electrophilic carbon of the imine, resulting in an intramolecular cyclization to benzimidazoline **93**. This benzimidazoline then undergoes a second dehydration, producing the desired benzimidazole **94**.



(adapted from Yang D, Fokas D, Li J, Yu L, Baldino CM. *Synthesis*. **2005**. 1, 47-56.)

Figure 36. Proposed route to benzimidazole via reductive cyclization

It is important to point out the importance of the partial reduction of the nitro group. Sodium dithionite has been shown to reduce nitro groups to amines in the presence of a strong acid. However, if the nitro group was completely reduced, the product would be in the wrong oxidation state to reach the required benzimidazole. Additionally, if the sodium dithionite could reduce the nitro group complete to the amine, it is possible an additional condensation with unreacted aldehyde could occur.

*3.4.3 Reductive cyclization of bromo-nitroaniline **66** with butyraldehyde*

Although, the use of sodium dithionite to perform a reductive cyclization on the 4-amino-3-methyl-4-nitrophenyl boronic acid pinacol ester (**75**) did provide some advantages over the first generation process, the yield for this sequence of reactions was still only moderate (60%). A modest yield can lead to significant cost increases, as less of the material is channeled down the desired pathway. One possibility to boost the yield of the

cyclization sequences, and thus reduce the associated cost, is to perform the boronation after benzimidazole formation.

Experiments reported earlier described the dehalogenation of the starting material (4-bromo-2-methyl-6-nitroaniline, **66**) during the attempted palladium catalyzed hydrogenation of the nitro group of an acylated derivative (**77**). However, the use of sodium dithionite provides a route to a benzimidazole performing the reduction in a manner compatible with the presence of the halogen[58]. Applying the reductive cyclization approach to the brominated nitroaniline **66** provides a convenient and high-yielding one-step route to benzimidazole formation (Figure 37). This reaction results in the generation of a previously unavailable intermediate (6-bromo-4-methyl-2-propyl-benzimidazole, **95**), which was isolated from the reaction mixture in a 97% a significant increase in yield over the analogous reaction with the boronated starting material (**83**).

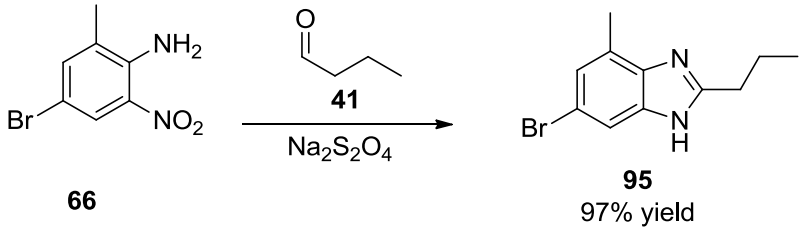


Figure 37. Formation of 6-bromo-4-methyl-2-propylbenzimidazole (**95**)

*3.4.4 Palladium catalyzed installation of boronate with pinacol diboron to benzimidazole **95***

With bromobenzimidazole **95** now available, a two-step process was used to convert **95** to the precursor target trifluoroborate **65**. Initially, pinacol diboron was again used to install the boron species and was inserted using 5 mol% of $PdCl_2$dppf to catalyze the reaction. In this case, the pinacol boronate **87** is not isolated or purified and is taken directly to the trifluoroborate using potassium bifluoride. These two-steps produced the desired

benzimidazole **65** in a 90% isolated yield from benzimidazole **95** (Figure 38). This improved process generates the central benzimidazole component in three steps with an overall yield of 87% from commercially available bromo-nitroaniline **66**. This is an improvement of 27% when compared to the 60% overall yield from the first generation process from the same starting material.

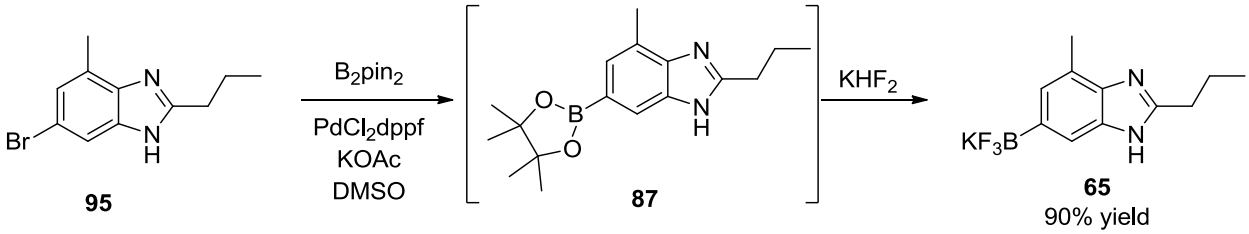


Figure 38. Two-step preparation of trifluoroborate **65** from benzimidazole **95** with pinacol diboron

3.4.5 Palladium catalyzed installation of boronic acid with diboronic acid

The reductive cyclization provided a much more efficient route to form the benzimidazole ring, greatly increasing the yield and eliminating the problematic three step sequence (amidation, palladium reduction, and cyclization) from the first generation process to make **65** from bromo-nitroaniline **66**. However, the synthetic sequence shown in Figure 38 is high yielding, it still relies on the use of a large excess of pinacol diboron to install the boron species. This pinacol diboron step has very poor atom economy as well, and it requires 5 mol% of $PdCl_2$dppf, which is not ideal.

In 2010, Molander reported a method for the use of diboronic acid ($B_2(OH)_4$) as a method to transform aryl chlorides into boronic acid derivatives and trifluoroborates.[59] To achieve this, Molander used 1-2.5 mol% of a palladium precatalyst developed by Buchwald in 2008,[60] along with the expensive ligand 2-dicyclohexylphosphino-2',4',6'-

triisopropylbiphenyl (XPhos). The palladium precatalyst then reacts with a diboronic acid ethyl ester formed *in situ* from the reaction of the diboronic acid and the ethanol used as a solvent. This diboronic acid ester reacts in a similar manner to the pinacol diboron and ultimately leads to the installation of the boron species. Without isolation the boronic acid ethyl ester can be transformed directly to a trifluoroborate or other boronic acid derivative (Figure 39).

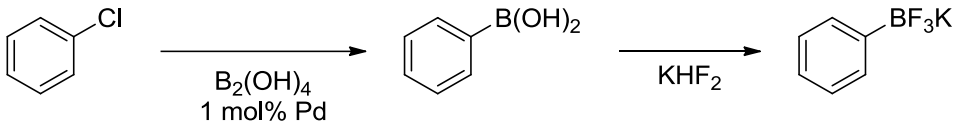
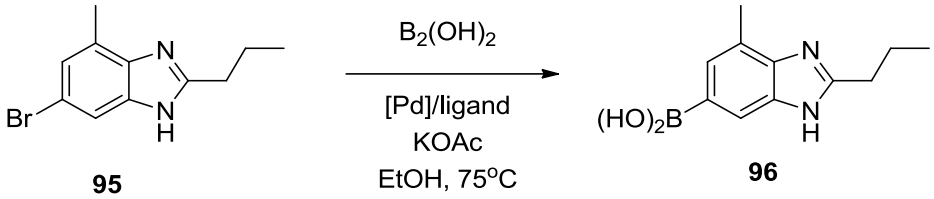


Figure 39. Molander preparation of trifluoroborates from aryl chlorides

Molander's approach using diboronic acid provides a more atom economical route to install the boron species to 6-bromo-4-methyl-2-propylbenzimidazole (**95**) with the potential to also decrease the amount of palladium needed to catalyze the reaction, thereby increasing reaction efficiency. Since bromides are typically more active than chlorides towards Suzuki reactions, efforts were focused on avoiding the inconvenient precatalyst and expensive ligand in favor of other catalyst and ligand systems (Table 6). While maintaining a similar catalyst loading (2 mol%) it was found that $PdCl_2$dppf with XPhos provided complete conversion to the boronic acid (**96**) in a short time (entry 3).

Table 6. Installation of boronic acid with diboronic acid and 6-bromo-4-methyl-6-propylbenzimidazole **95**



95 **96**

entry[a]	catalyst	ligand	time	96[b]
1	2 mol% $Pd(OAc)_2$	XPhos	15 h	23
2	2 mol% $PdCl_2$dppf	none	15 h	75
3	2 mol% $PdCl_2$dppf	XPhos	5 h	100 (93%)[c]
4	2 mol% $PdCl_2$dppf	PPh_3	5 h	90 (83%)
5	2 mol% Pd_2dba_3	PPh_3	15 h	85
6	2 mol% $PdCl_2(PPh_3)_2$	none	15 h	78
7	2 mol% $PdCl_2(PPh_3)_2$	XPhos	5 h	100
8	2 mol% $PdCl_2(PPh_3)_2$	PPh_3	15 h	80

[a] **95** (100 mg,0.40 mmol), $B_2(OH)_4$ (106 mg, 1.2 mmol), KOAc (116 mg, 1.2 mg)
[b] Relative peak area determined by HPLC
[c] Values in parentheses represent isolated yield after transformation to trifluoroborate

When carried forward to the trifluoroborate, this system produced an isolated yield of 93%. This was promising, but ultimately still utilized a more expensive palladium catalyst and ligand. Using the same catalyst ($PdCl_2$dppf) and a much less expensive ligand (triphenyl phosphine, PPh_3) the reaction still proceeded, but with a lower isolated yield of 83% when carried on to the trifluoroborate (table 6, entry 4). Next, a less expensive alternative to $PdCl_2$dppf was tested. Bis(triphenylphosphine)palladium (II) dichloride

($PdCl_2(PPh_3)_2$) provided complete conversion to the boronic acid when paired with XPhos (entry 7) and an 80% conversion when used with PPh_3 (entry 8). Despite the lower conversion for the $PdCl_2(PPh_3)_2/PPh_3$ conditions, they still provided a more economical process to prepare the trifluoroborate and were further examined in more detail.

3.4.6 Dosing experiments and optimization of boronation reaction

The $PdCl_2(PPh_3)_2/PPh_3$ system was then monitored over time. In initial experiments, both 1 mol% and 2 mol% catalyst loading levels were tested, and in both cases the catalyst appeared to be deactivated after only 8 hours. In an attempt to drive the reaction even further, an additional dose of catalyst and ligand was added to each reaction and a subsequent modest increase in product formed was observed (Figure 40).

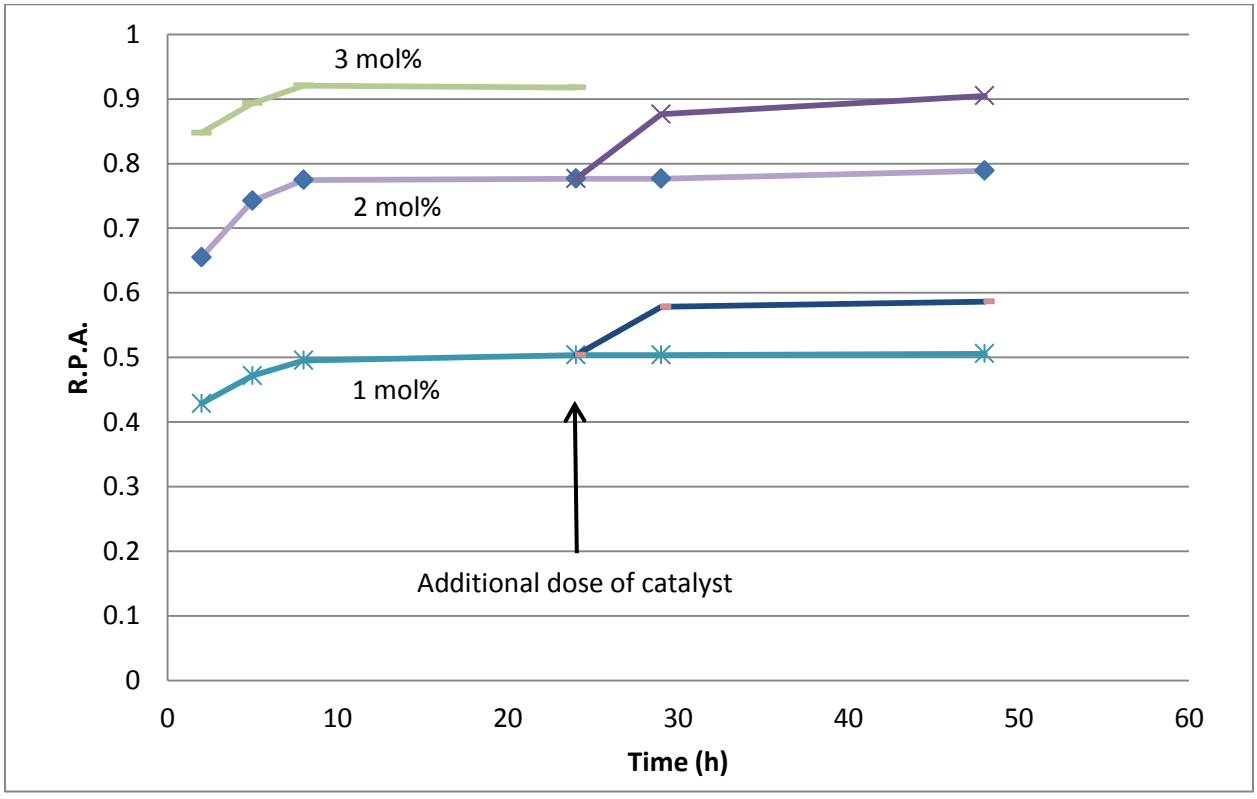
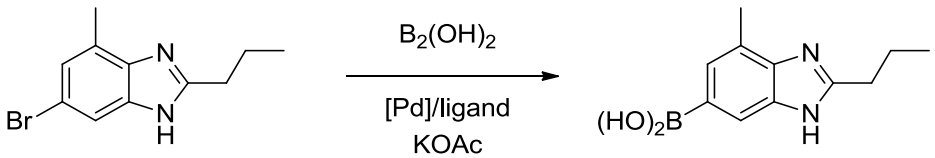


Figure 40. Dosing experiments of boronation reaction with diboronic acid

Even after the second dose of catalyst the 1 mol% reaction (now containing a total of 2 mol% catalyst), showed a lower conversion than the reaction than originally was charged with 2 mol% did after only 8 hours (Table 7, entries 2 and 3). It was also noted that increased palladium loading at the beginning of the reaction resulted in a significant increase in conversion. Finally, that information was used to leverage the tendency for the reaction to occur more rapidly earlier in the reaction. Initial palladium loading was increased to 3 mol% and an even higher conversion was observed (Figure 40, top line). After 8 hours the 3 mol% reaction produced the boronic acid intermediate (**96**) with a conversion of 93% and a 90% isolated yield when carried forward to the trifluoroborate salt (Table 7, entry 5).

Table 7. Effect of catalyst loading on installation of boronation of **95** with diboronic acid



95 **96**

entry[a]	catalyst	ligand	time	96[b]
1	1 mol% $PdCl_2(PPh_3)_2$	PPh_3	8 h	50
2	1 mol% $PdCl_2(PPh_3)_2$	PPh_3	48 h[d]	59
3	2 mol% $PdCl_2(PPh_3)_2$	PPh_3	8 h	77
4	2 mol% $PdCl_2(PPh_3)_2$	PPh_3	48 h[d]	90
5	3 mol% $PdCl_2(PPh_3)_2$	PPh_3	8 h	93 (90%)[c]

[a] **95** (100 mg,0.40 mmol), $B_2(OH)_4$ (106 mg, 1.2 mmol), KOAc (116 mg, 1.2 mg)
[b] Relative peak area determined by HPLC
[c] Values in parentheses represent isolated yield after transformation to trifluoroborate
[d] Second dose of catalyst added at 24 h.

The 3 mol%, the $PdCl_2(PPh_3)_2/PPh_3$ system (Figure 41), despite a slightly higher catalyst loading and slightly lower yield, still provides a more economical approach to prepare potassium (4-methyl-2-propylbeznimidazol-6-yl) trifluoroborate (**65**). When compared to the boronation reaction with pinacol diboron, diboronic acid provides a more atom economical boron substitute while requiring less of a cheaper catalyst (3 mol% $PdCl_2(PPh_3)_2$ vs. 5 mol% $PdCl_2$dppf) to produce potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate (**65**) with overall yield of 90% over two transformations.

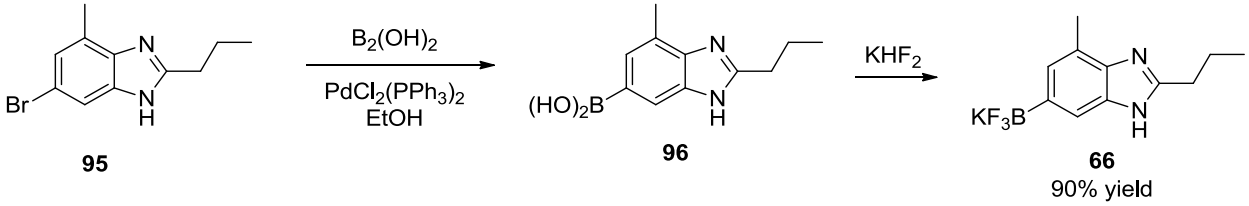


Figure 41. Two-step preparation of trifluoroborate **69** from benzimidazole **95** with diboronic acid

3.4.7 Formation of benzimidazole 65 from 66 with no isolated intermediates

Again, trifluoroborate **65** was formed directly from the bromo-nitroaniline **66** without any intermediate isolation. This new process completes all three steps (reductive cyclization, boronic acid installation and conversion to trifluoroborate) to produce the desired benzimidazole component (**65**) and can easily be isolated in pure form. This telescoped strategy leads to an improved isolated yield of 90% (Figure 42). This new route addresses the major issues associated with the first generation cyclization while greatly increasing the yield.

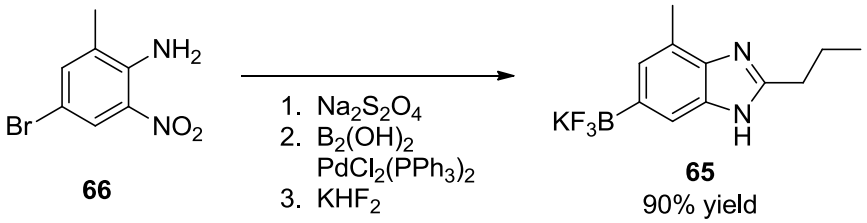


Figure 42. Three-step preparation of trifluoroborate **65** from bromo-nitroaniline **66.**

CHAPTER IV

PREPARATION OF TELMISARTAN

4.1 Background

Most of the previously reported telmisartan syntheses prepared telmisartan by cyclization of each benzimidazole sequentially, followed by the installation of the biphenyl group. This strategy suffers from significant impurities often related to the formation of the benzimidazole components.[61] The highly selective Suzuki cross-coupling reaction envisioned provides an alternative as the key step in our total synthesis. This approach is highly tolerant of a wide variety of functional groups, giving larger flexibility throughout the synthesis with the potential to significantly reduce impurities.

4.1.1 Impurities associated with traditional approach

The impurities from the original approach are most often associated with the problematic condensation between 4-methyl-2-propylbenzimidazole-6-carboxylic acid (**13**) and *N*-methyl-o-phenylene diamine (**9**). This reaction is run at elevated temperatures for an extended period of time in PPA (Figure 43). The condensation produces the functionalized benzimidazole (**10**), but the harsh conditions can lead to many difficult-to-remove impurities.

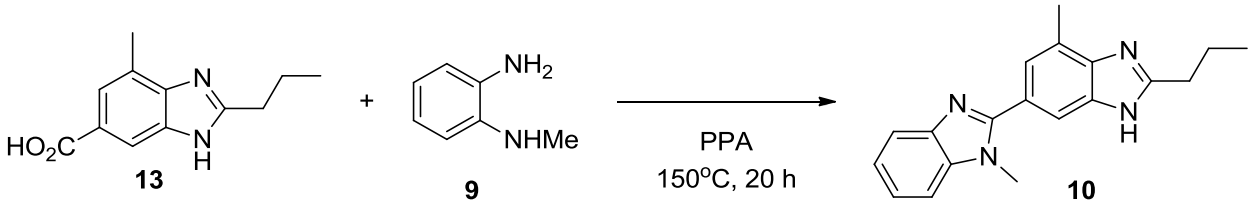


Figure 43. Problematic condensation reaction from Ries synthesis

As the impurities are difficult to remove, they are often carried forward to downstream steps. Most of the impurities in the final telmisartan product are associated with this condensation (Figure 44). Because the reaction only produces a 64% yield, there is likely a small amount of unreacted **13**, that if present during the subsequent alkylation and hydrolysis steps could produce 1-((2'-carboxy-[1,1'-biphenyl]-4-yl) methyl)-4-methyl-2-propylbenzimidazole-6-carboxylic acid (**98**). However, there are a lot of impurities that stem from the *N*-(2-aminophenyl)-4-methyl-2-propylbenzimidazole-6-carboxamide (**97**), an impurity that likely arises from the presence of unmethylated *o*-phenylene diamine that does not completely undergo cyclization. The impurity **97** can also lead to 7'-methyl-2'-propyl-2,6'-dibenzimidazole (**99**) upon cyclization of the unalkylated o-aminophenyl amide. Similar to **98**, dibenzimidazole **100** can be produced by subsequent alkylation and hydrolysis leading to addition of the biphenyl moiety at both the 1- and 1'-position of the dibenzimidazole.

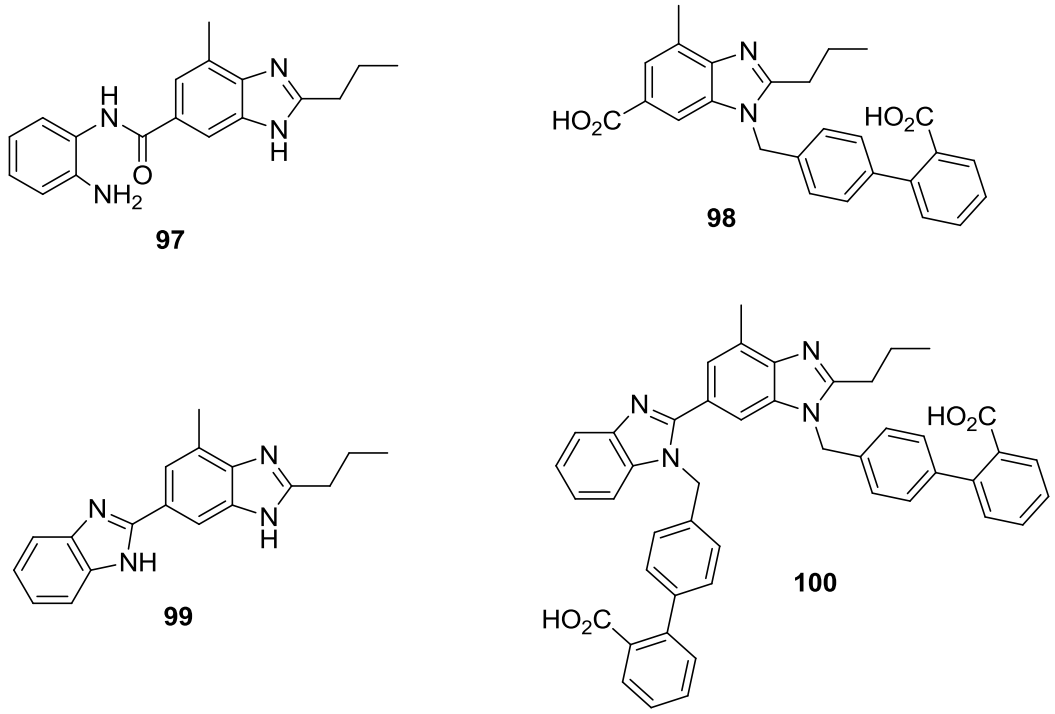


Figure 44. Common impurities from Ries Synthesis

4.1.2 Previous attempt at synthesis of telmisartan via simultaneous ring closures

Prior to exploring the Suzuki reaction, an alternative route to form the dibenzimidazole was investigated (Figure 45). The goal of this synthesis was to improve upon the efficiency of the original approach by simultaneously forming both benzimidazole rings. This scheme utilizes a similar approach to the Wen patent synthesis, but varied the method used to form the diamide species (**43**) and perform the concurrent ring closures.

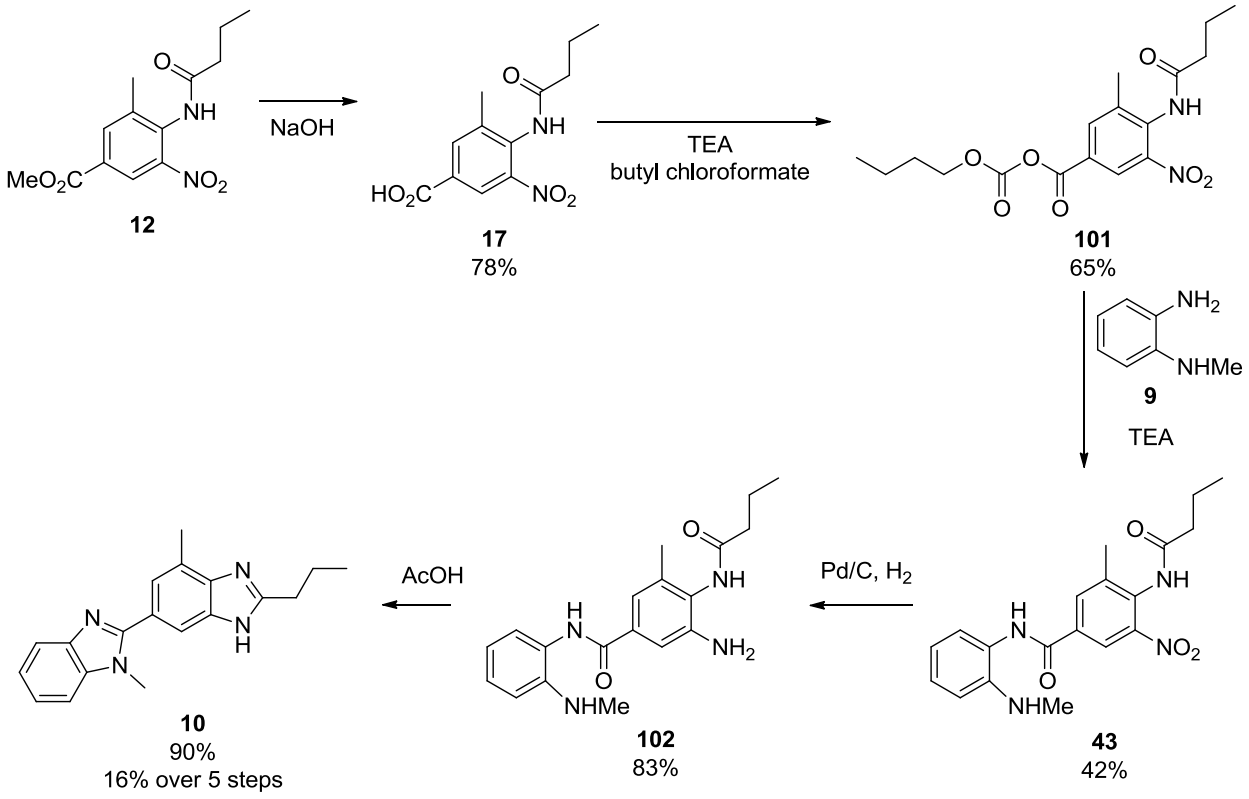


Figure 45. Formation of dibenzimidazole 10 via simultaneous ring closures

Starting from commercially available methyl-4-butyramido-3-methyl-5-nitrobenzoate (**12**), the methyl ester was hydrolyzed using sodium hydroxide producing 4-butyramido-3-methyl-5-nitrobenzoic acid (**17**) with a yield of 78%. Instead of using an expensive coupling agent to form the amide with the *N*-methyl-*o*-phenylene diamine (**9**), butyl chloroformate was used to form the mixed anhydride **101** providing a moderate yield of 65%. The isolated anhydride was then condensed with **9** to produce the nitro diamide **43** with a low yield of 42%. However, with the nitro diamide structure formed, the penultimate reduction of the nitro group (to produce **102**) and subsequent cyclization both proceeded with reasonable yields (83% and 90%, respectively). This work showed some promise as a viable route to produce the common dibenzimidazole intermediate (**10**) with the final steps reacting in high yields. Significant improvements of early reaction steps would be required in order to make

the approach a more realistic alternative. As it stands, this process produces the dibenzimidazole intermediate **10** with only a 16% yield over 5 steps.

4.2 Suzuki cross-coupling reactions

A major component of the approach from the proposed retrosynthetic analysis relies on a Suzuki-Miyaura cross-coupling reaction to form the dibenzimidazole linker. The Suzuki reaction has found utility across a wide range of chemistry, from use in polymers[62], agriculture[63], pharmaceuticals[64] and even the synthesis of complex natural products[65]. Many advantages are also associated with the Suzuki reaction over other cross-coupling reactions.[66] These reactions typically are performed using milder conditions while using less toxic reagents. Additionally, boronic acid derivatives provide easily removable inorganic byproducts. Most importantly, the Suzuki reaction can tolerate most functional groups and even remain active in the presence of water.

4.2.1 Suzuki cross-coupling catalytic mechanism

The Suzuki-Miyaura reaction proceeds through a catalytic cycle containing four major steps that ultimately lead to the formation of a new carbon-carbon bond (Figure 46). The first step is the oxidative addition of an aryl halide to a palladium (0) complex (**103**). Palladium insertion occurs between the aryl group and the halide substituent forming a palladium (II) species (**104**). At this point, the palladium complex under goes a base mediated metathesis replacing the halide with the anion of the base (**105**).

Simultaneously, the organoboron **107** must first be transformed into the corresponding organoborate (**108**) by the addition another equivalent of the base. This activated boron compound can then undergo transmetallation placing both aryl species on the same palladium atom (**106**) releasing the inorganic byproduct **109**. After

transmetallation the palladium (II) complex **106** then undergoes reductive elimination, releasing the newly formed biaryl product and regenerating a palladium (0) complex that can proceed to catalyze the formation of other carbon-carbon bonds in the reaction mixture.

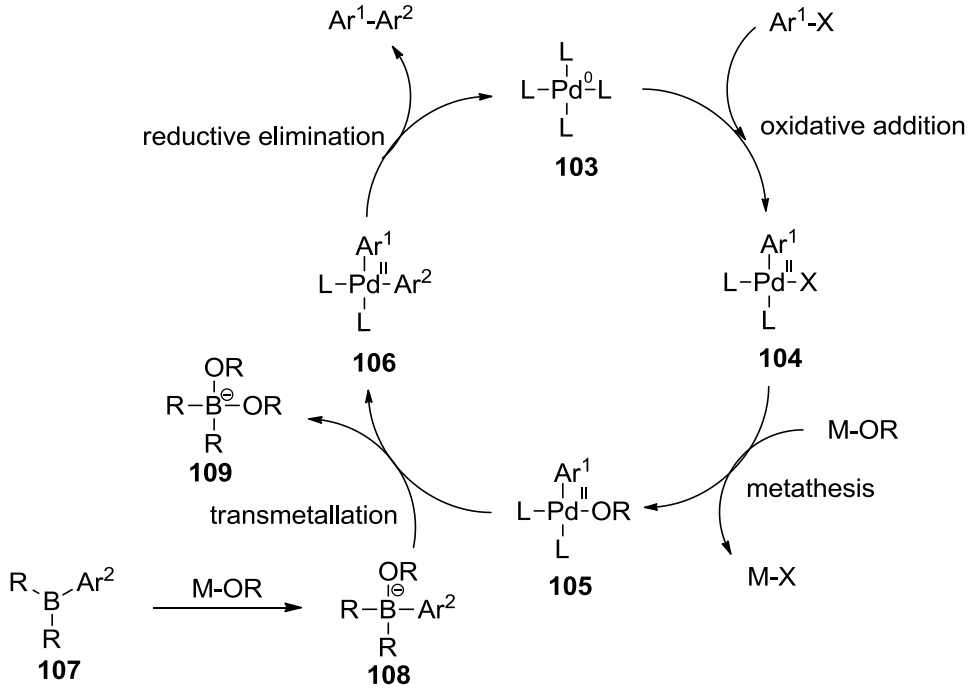


Figure 46. Suzuki cross-coupling reaction mechanism

4.2.2 Suzuki proof of concept reactions with 2-bromo-1-methylbenzimdazole

Prior to the work done on this project, a Suzuki reaction had not ever been reported that includes the reaction of a bromide at the 2-position of a benzimidazole. Before exploring the more advanced chemical systems, a few proof of concept reactions were completed to demonstrate the viability of 2-bromo-1-methylbenzimidazole (**54**) as a potential candidate for the preparation telmisartan. The first reaction completed was the coupling of halide **54** with the phenyl boronic acid (**110**) (Figure 47). This reaction, catalyzed

by palladium acetate with a triphenyl phosphine ligand, led to a relative conversion of 98% to the desired 1-methyl-2-phenylbenzimidazole (**111**).

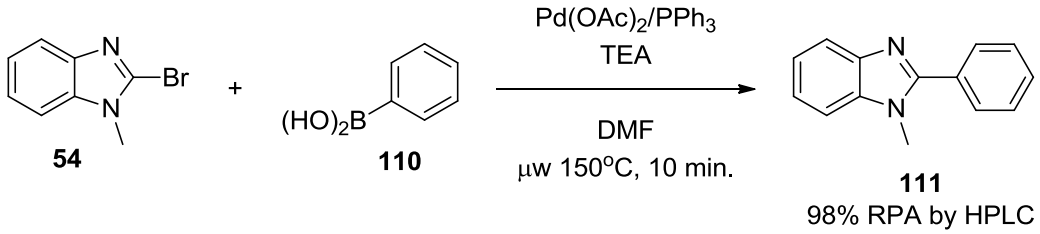


Figure 47. Suzuki reaction of 2-bromo-1-methylbenzimidazole and phenyl boronic acid

The successful coupling at the 2-position of benzimidazole **54** with the simple boronic acid was very promising. The same reaction was attempted with a more functionalized system (Figure 48). Commercially available 4-amino-3-nitrophenyl boronic acid pinacol ester (**112**) was chosen as the next coupling partner due to its similarity with the nitroaniline target (**83**) described earlier. The reaction proceeded to produce the desired 2-(4-amino-3-nitrophenyl)-1-methylbenzimidazole (**113**) with high relative conversion.

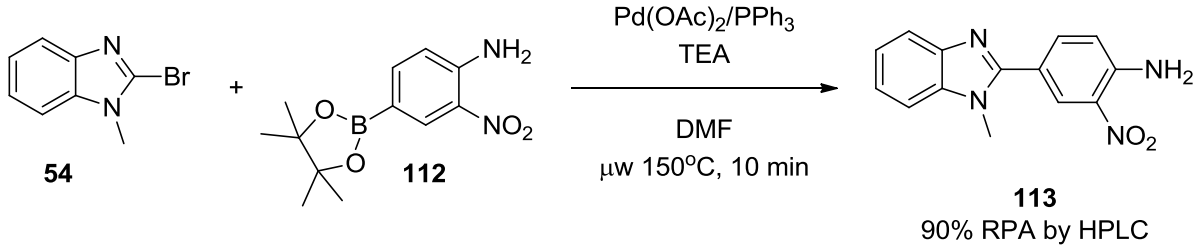


Figure 48. Suzuki reaction between benzimidazole **54** and nitroaniline **112**

With the promising results in hand from the proof of concept studies, the strategy was applied to authentic telmisartan precursors. One route envisioned involved the formation of 2-(4-amino-3-methyl-5-nitrophenyl)-1-methylbenzimidazole (**40**) by coupling

benzimidazole **54** with (4-amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (**83**) (Figure 49). When this was attempted, the reaction led to a reasonable relative conversion (80%) to the desired coupling product **40** proving that the Suzuki is a viable method to form the carbon-carbon linker between the two dibenzimidazoles of telmisartan.

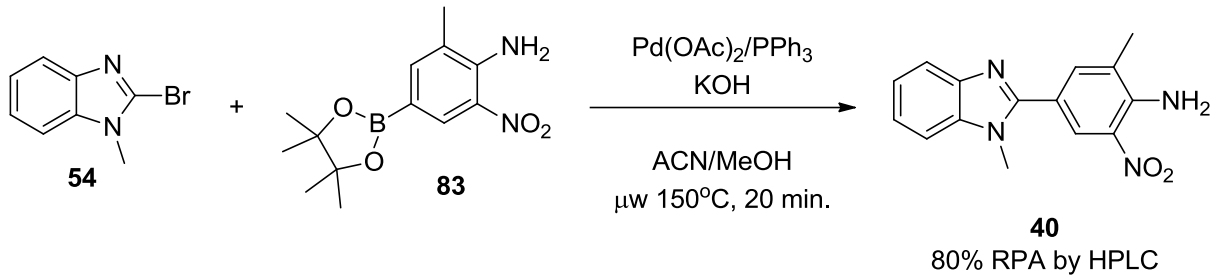


Figure 49. Suzuki reaction of benzimidazole **54** and nitroaniline **83**.

It is presumed that the nitroaniline **40** could be transformed to the dibenzimidazole, carried forward through any of the previously described methods for the formation of benzimidazoles from o-nitroanilines. However, due to the moderate conversion and the problems associated with the cyclization method historically used to construct telmisartan (the amidation, reduction and acid cyclization), this route was not explored further in favor of more promising avenues.

*4.2.3 Suzuki reaction of benzimidazoles **54** and **83***

The next route attempted involved performing a Suzuki reaction with the two benzimidazoles components already formed. This strategy would minimize the impact of any yield loss during benzimidazole cyclization on the cost associated with the palladium catalyst required for the Suzuki reaction. This route also targets the primary dibenzimidazole intermediate (**10**), which serves as the starting material for the commercial process. Dibenzimidazole **10** is formed by coupling 2-bromo-1-methylbenzimidazole (**54**)

and 4-methyl-2-propylbenzimidazol-6-yl boronic acid pinacol ester (**83**) (Figure 50). However, this reaction only produced the desired benzimidazole (**10**) with relatively low conversion, and a significant amount of byproduct was observed.

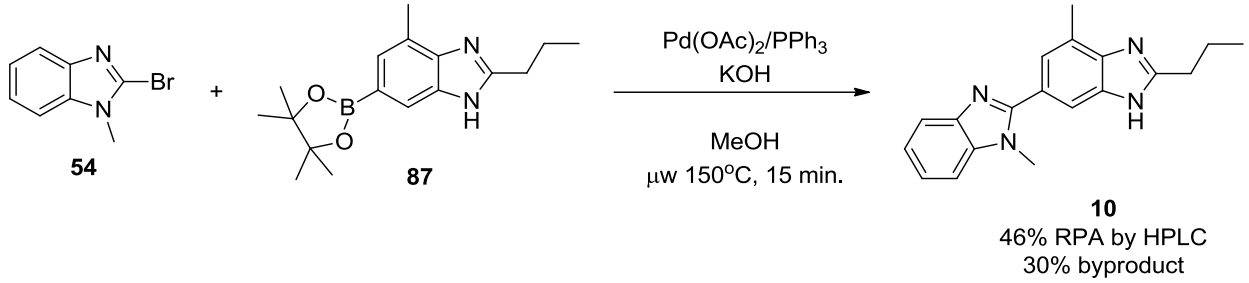


Figure 50. Suzuki reaction of benzimidazoles **54** and **83**

When investigated further mass analysis led to the conclusion that the reaction was also resulting in a 1,2'-dibenzimidazole **114** (Figure 51). It is proposed that the bromide of **54** undergoes a nucleophilic substitution with the deprotonated nitrogen at the 1-position of benzimidazole **87**. Left unprotected, the nucleophilic nitrogen of **87** is susceptible to this type of reactivity. These observations were leveraged later in the process for the installation of the biphenyl moiety, achieved via nucleophilic substitution of a biphenyl halide.

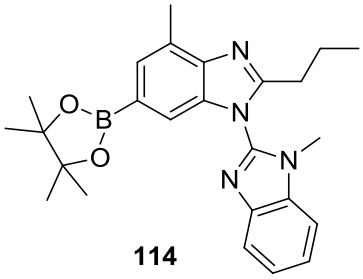


Figure 51. Proposed byproduct from Suzuki to form dibenzimidazole **10**

4.3 First generation preparation of telmisartan with biphenyl carbonitrile

4.3.1 Alkylation to install biphenyl carbonitrile component

Instead of using a protecting group it was hypothesized that installing the biphenyl moiety prior to the Suzuki reaction would preclude the unwanted byproduct. The biphenyl group would eliminate the presence of the removable proton at the 1-position of the central benzimidazole, without requiring additional protection and deprotection reactions to perform the Suzuki reaction. In order, to proceed in the most expeditious manner possible, the installation was performed using a strategy similar to the current commercial process.

Prior to introducing the biphenyl halide, potassium *tert*-butoxide (KO*t*Bu is used to deprotonate the 1-postion of potassium (4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate (**65**). The biphenyl is installed using 4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile (**41**). The *N*-alkylation reaction occurs at room temperature and produces potassium (1-((2'-cyano-[1,1'-biphenyl]-4-yl)-methyl)-4-methyl-2-propylbenzimidazol-6-yl) trifluoroborate (**115**). This process provides the desired product (**115**) with an isolated yield of 90% (Figure 52). Notably, it was found to be necessary to pretreat the benzimidazole **65** with the base in order to avoid the formation of unwanted Williamson ether byproducts.

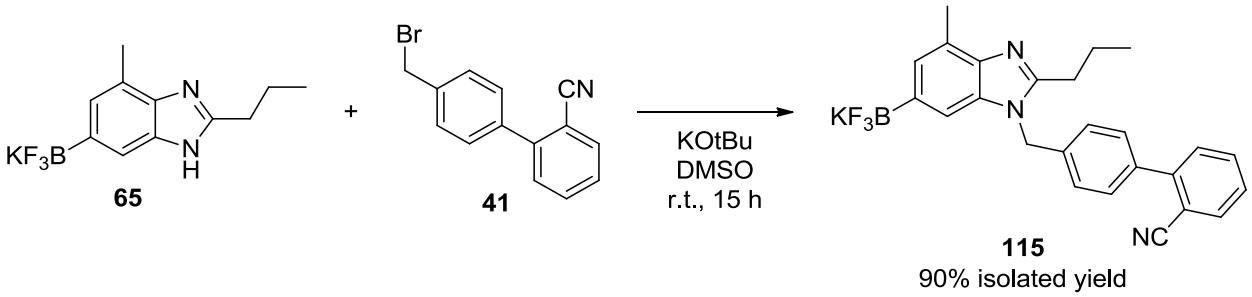


Figure 52. Alkylation of benzimidazole **65** with biphenyl nitrile **41**

*4.3.2 Suzuki reaction of benzimidazoles **54** and **115***

With the biphenyl benzimidazole and trifluoroborate components in place, compound **115** was then successfully coupled with 2-bromo-1-methylbenzimidazole (**54**). This was the first case when the Suzuki reaction successfully formed the dibenzimidazole linker without any major complications. Using $PdCl_2dppf$, the two benzimidazoles were combined producing the nitrile of telmisartan (**46**) in high yield (Figure 53). In only a short period of time (10 minutes), under microwave irradiation at 120°C the reaction achieved a 91% isolated yield.

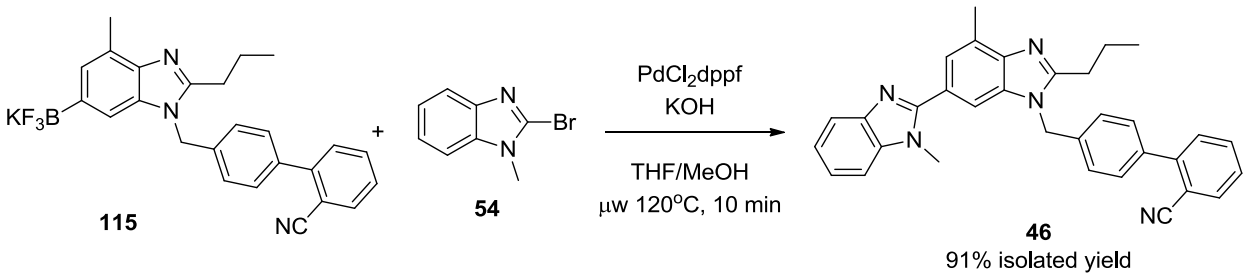


Figure 53. Suzuki reaction of benzimidazoles **54** and **115**

*4.3.3 Hydrolysis of nitrile **115** to form telmisartan*

Finally, with the nitrile of telmisartan (**46**) in hand there remained only one transformation to complete the synthesis utilizing the new disconnection approach featuring the Suzuki reaction between two different functionalized benzimidazoles. This final step was the hydrolysis of the nitrile to produce the carboxylic acid (Figure 54). Using the method described in the commercial process, the nitrile (**46**) undergoes hydrolysis using KOH and 150°C for 15 hours. After acidification with AcOH, this yielded telmisartan (**1**) with an isolated yield of 60%.

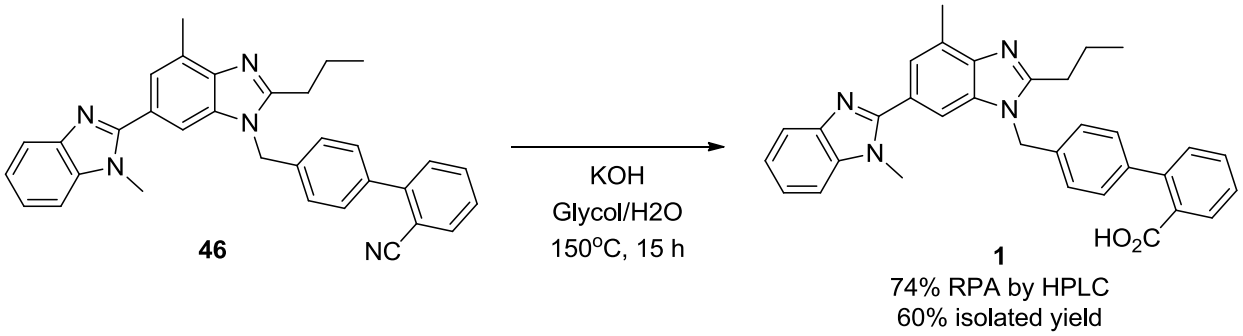


Figure 54. Nitrile hydrolysis to form telmisartan

4.3.4 First generation three-step preparation of telmisartan using biphenyl carbonitrile

Although, this step used in the commercial process, there are several notable disadvantages. In the experiments performed, the reaction did not proceed all the way to the carboxylic acid. A significant amount of the amide (an intermediate in the hydrolysis) was present in the final reaction mixture and was difficult to remove completely from the product. This process also relies on high temperatures and long reaction times. These two aspects are unfavorable when considering the ultimate goal of completing the synthesis of telmisartan in flow. However, this method constituted the first time that telmisartan (**1**) was produced using a Suzuki reaction to form the dibenzimidazole linker. This approach provided an overall yield of 49% from the benzimidazole precursors (Figure 55).

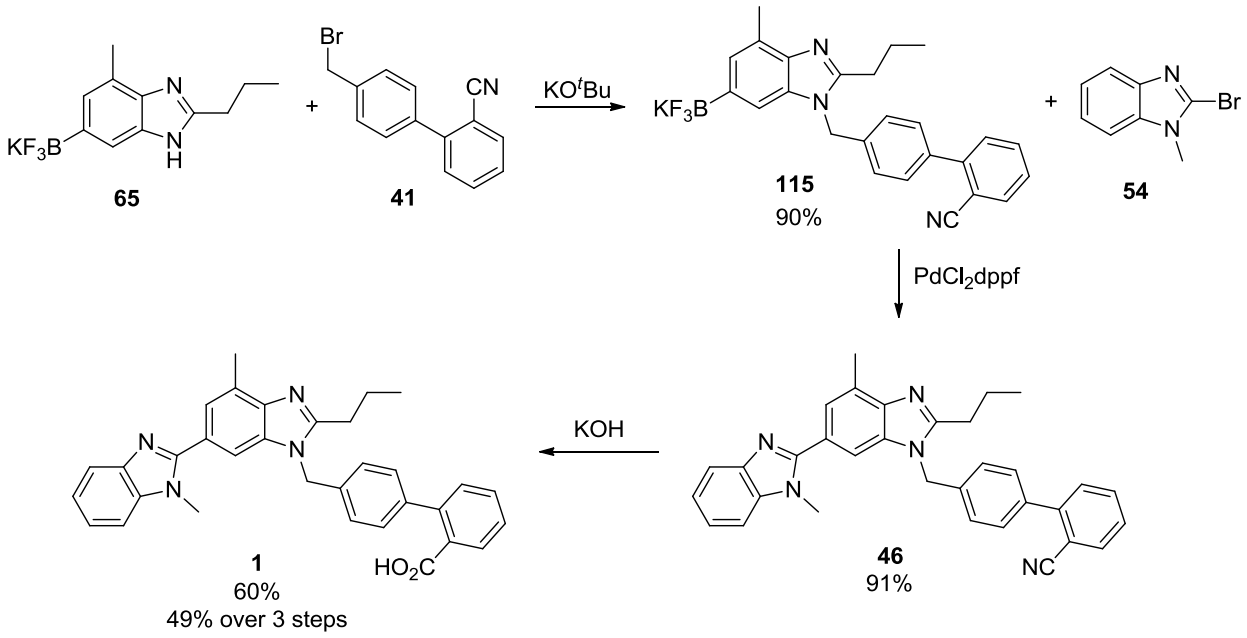


Figure 55. Three-step preparation of telmisartan using nitrile

4.4 Second generation preparation of telmisartan with biphenyl methyl ester

4.4.1 One-pot alkylation and hydrolysis using methyl ester

With the previous approach, the Suzuki reaction was shown to be a valid strategy for assembling telmisartan; however, the use of the nitrile introduced some issues that could be mitigated by finding an alternative biphenyl component. Instead of the nitrile, the analogous methyl ester, methyl-4'-(bromomethyl)-[1,1'-biphenyl]-2-carboxylate (**14**), was elected as an alternative with the potential for resolving the issues related to the hydrolysis to form the final carboxylic acid. Again, the *N*-alkylation was performed using potassium *tert*-butoxide as a base. The alkylation of benzimidazole **65** with the biphenyl **14** was found to proceed quickly, producing the methyl ester (**116**) with excellent conversion.

It was also found that, if the reaction was allowed to stir for an extended time, the carboxylic acid would start to appear in the reaction mixture. With even a small amount of water present in the solvent, the potassium *tert*-butoxide can react to form potassium

hydroxide, which can in turn hydrolyze the methyl ester of **116**. Instead of developing a method to discourage the formation of the carboxylic acid, the direct alkylation product was not isolated but rather a solution of aqueous potassium hydroxide was introduced to facilitate hydrolysis (Figure 56). These two telescoped steps provided the desired carboxylic acid (**117**) in a high yield of 93%. This process constitutes a high-yielding and streamlined route to the desired carboxylic acid.

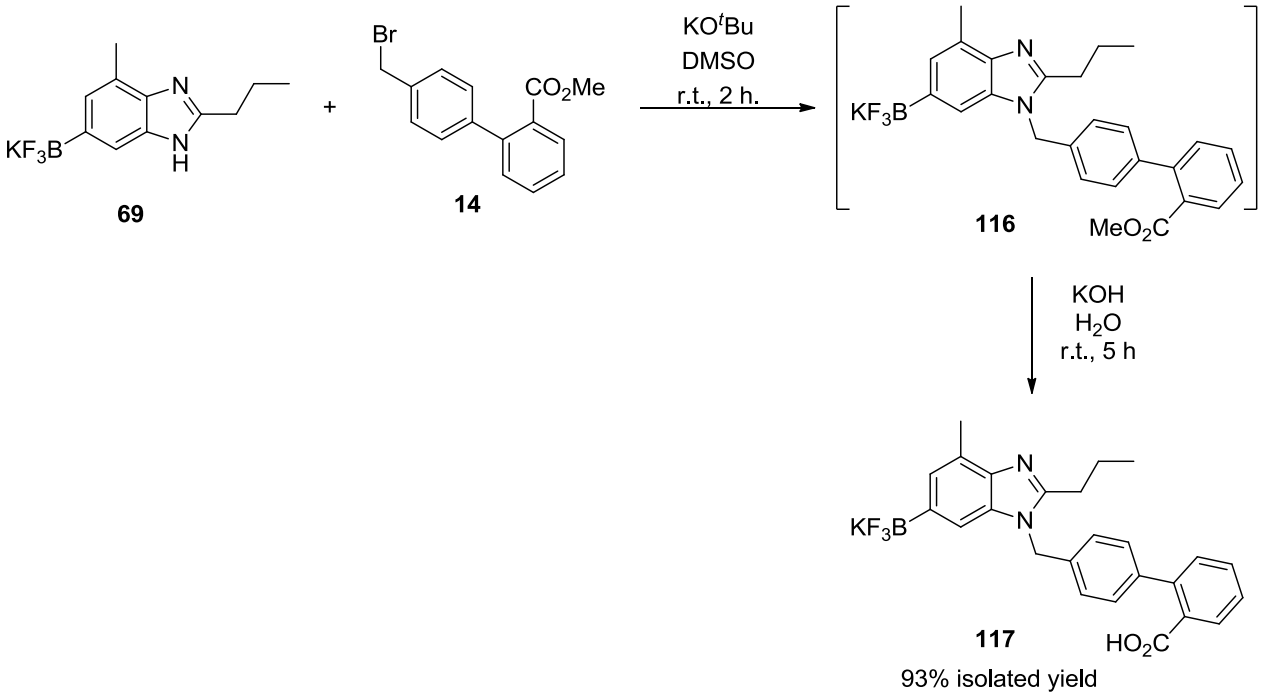


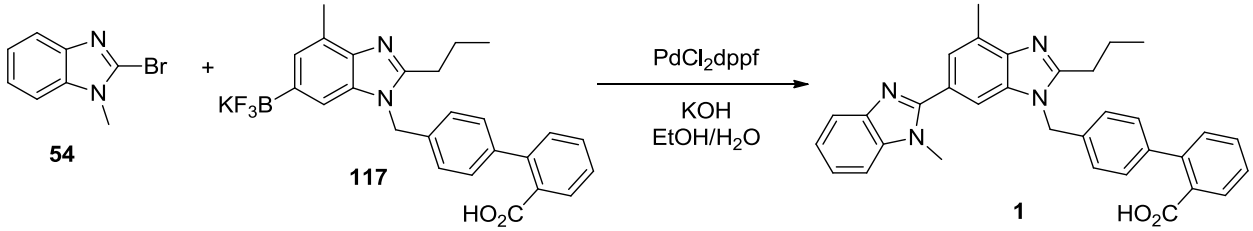
Figure 56. Two-step telescoped alkylation and hydrolysis to form benzimidazole **117**

*4.4.2 Suzuki reaction of benzimidazole **54** and **117** to produce telmisartan*

Finally, with the biphenyl moiety introduced and the hydrolysis complete, the final coupling reaction of bromide **54** and trifluoroborate **117** was the only remaining step to be explored. In order optimize the yield and efficiency of the process, a number of reactions were run. A factorial design of experiment (DOE) was undertaken to identify the set of reaction parameters that would maximize yield while minimizing catalyst loading. The other

two factors tested were temperature and microwave irradiation time (Table 8). Using $PdCl_2$dppf as the catalyst the reactions were run in 50% ethanol solution with KOH as the base.

Table 8. Microwave assisted DOE of Suzuki cross-coupling to form telmisartan



entry[a]	catalyst loading (mol%)	conditions	1[b]
1	2	80°C, 5 min.	17
2	10	80°C, 5 min.	56
3	2	150°C, 5 min.	66
4	10	150°C, 5 min.	91
5	5	120°C, 10 min.	85
6	2	80°C, 15 min.	27
7	10	80°C, 15 min.	72
8	2	150°C, 15 min.	76
9	10	150°C, 15 min.	92
10	2	150°C, 30 min.	89
11	10	150°C, 30 min.	95
12	5	150°C, 30 min.	88
13	5	120°C, 30 min.	82

[a] **54** (0.19 mmol), **117** (0.20 mmol), 4 mL H_2O/EtOH (1:1 mixture). [b] Isolated yield

As expected, it was found that all three had a direct correlation with the yield of the reaction (Figure 57). The reaction with highest catalyst loading tested (10 mol%) produced the best yield (95%) when reacted at 150^{o}C for 30 minutes under microwave irradiation (entry 11). However, using the high catalyst loading is not the most economical approach despite the highest yield. Lowering the catalyst loading all the way down to 2 mol% (entry 10) the reaction still produced a high yield of 89%. The significant decrease in catalyst loading only led to a small decrease in yield, making it a more favorable route when taking cost considerations into account.

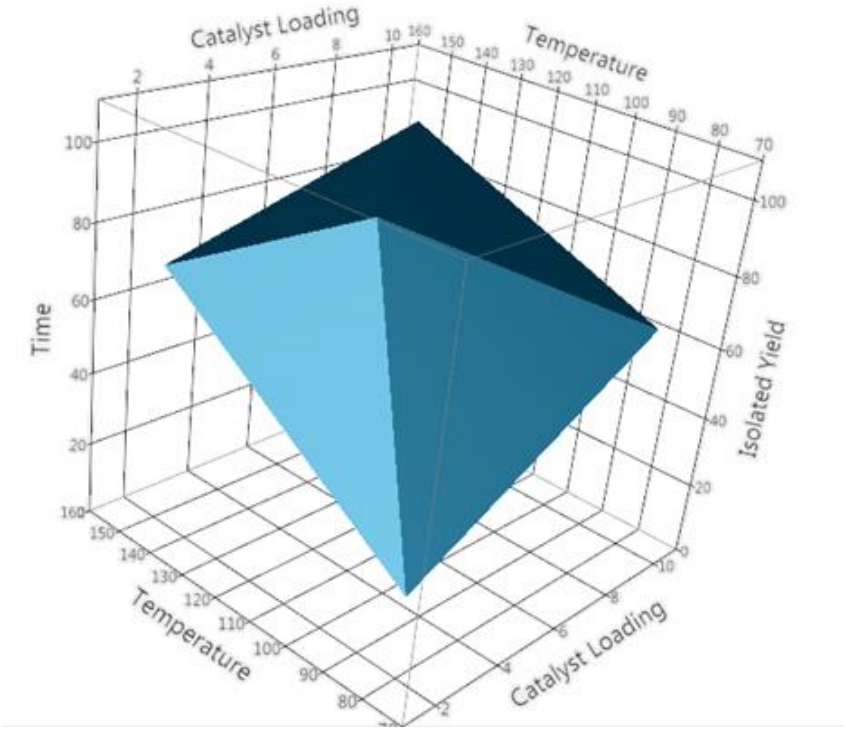
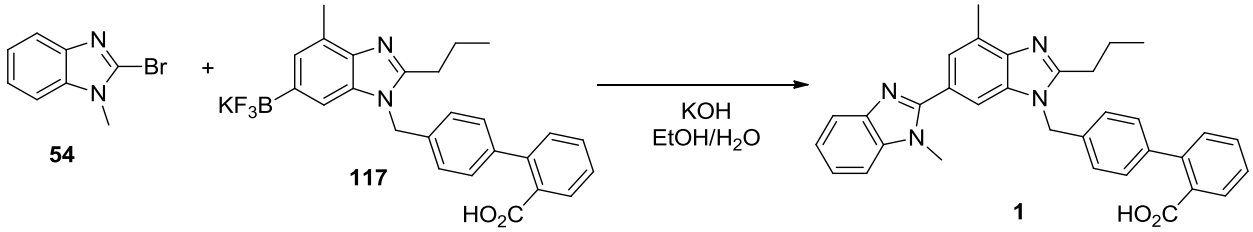


Figure 57. DOE of Suzuki cross-coupling to form telmisartan

With the microwave reaction conditions well established, the second set of reactions explored different palladium catalysts and ligands commonly used for the Suzuki cross-

coupling reaction (Table 9). All the catalysts tested produced reasonable yields above 60%. In this case the catalyst used for the DOE provided the best yield of 89% (entry 1).

Table 9. Catalyst screen of Suzuki cross-coupling to form telmisartan



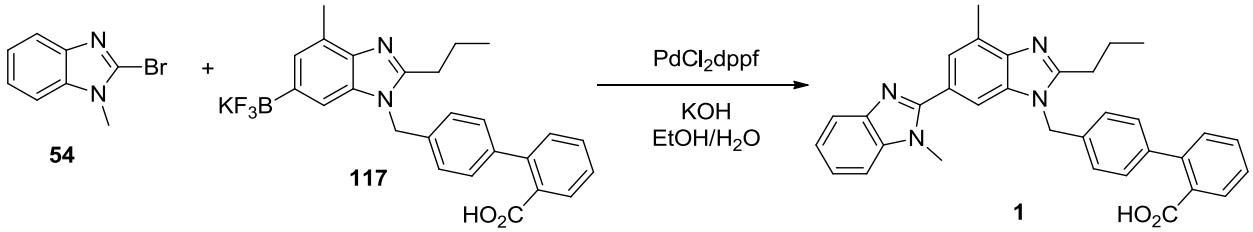
entry[a]	catalyst	ligand	conditions	1[b]
1	2 mol% $PdCl_2dppf$	n/a	150°C, 30 min.	89
2	2 mol% $PdCl_2(PPh_3)$	n/a	150°C, 30 min.	78
3	2 mol% $Pd_2(dba)_3$	n/a	150°C, 30 min.	68
4	2 mol% $Pd(OAc)_2$	6 mol% PPh_3	150°C, 30 min.	76
5	2 mol% $Pd(OAc)_2$	6 mol% XPhos	150°C, 30 min.	62

[a] **54** (0.19 mmol), **117** (0.20 mmol), 4 mL H_2O/EtOH (1:1 mixture). [b] Isolated yield

With the optimum catalyst and reaction conditions determined utilizing microwave technology, conditions were explored to determine feasibility under conventional heating conditions (Table 10). However, with the ethanol/water solvent system the reflux temperature is around 80^{o}C which is significantly lower than temperatures achieved in the sealed tube of the microwave reactor. From the DOE it was found that the higher temperatures lead to much improved yields. Even when the conventional system ran for a much longer period of time (15 h) it produced low yields. The 2 mol% reaction produced

only a 36% yield (entry 1). The 10 mol% reaction increased the yield up to 55% (entry 2), however this result was still suboptimal when compared to the 89% and 95% yields from the respective microwave reactions (entries 3 and 4). It is anticipated that, in a pressurized system that could reach the elevated temperatures, conventional heating would produce higher yields than observed with atmospheric reflux conditions.

Table 10. Comparing conventional heating to microwave heating



entry[a]	catalyst	conditions	1[b]
1	2	reflux, 15 h	36
2	10	reflux, 15 h	55
3	2	μw 150°C, 30 min	89
4	10	μw 150°C, 30 min	95

[a] **54** (0.19 mmol), **117** (0.20 mmol), 4 mL H_2O/EtOH (1:1 mixture). [b] Isolated yield

4.4.3 Second generation three-step preparation of telmisartan

This approach, based on a key disconnection between intact benzimidazoles, exploits a Suzuki cross-coupling reaction to establish a concise, convergent synthesis and high yielding synthesis of telmisartan. This process remedies the difficult hydrolysis of the nitrile and replaces it with a very simple de-esterification of the methyl ester, while still providing a route that still allows for the highly reactive Suzuki reaction. Using the optimized

Suzuki conditions the overall yield for the three-step preparation of telmisartan is 83% (Figure 58). The overall yield for the entire process, when accounting for the preparation of the precursor from 4-bromo-2-methyl-6-nitroaniline (**66**), is 74% which great improves on even the most recently reported syntheses of telmisartan.

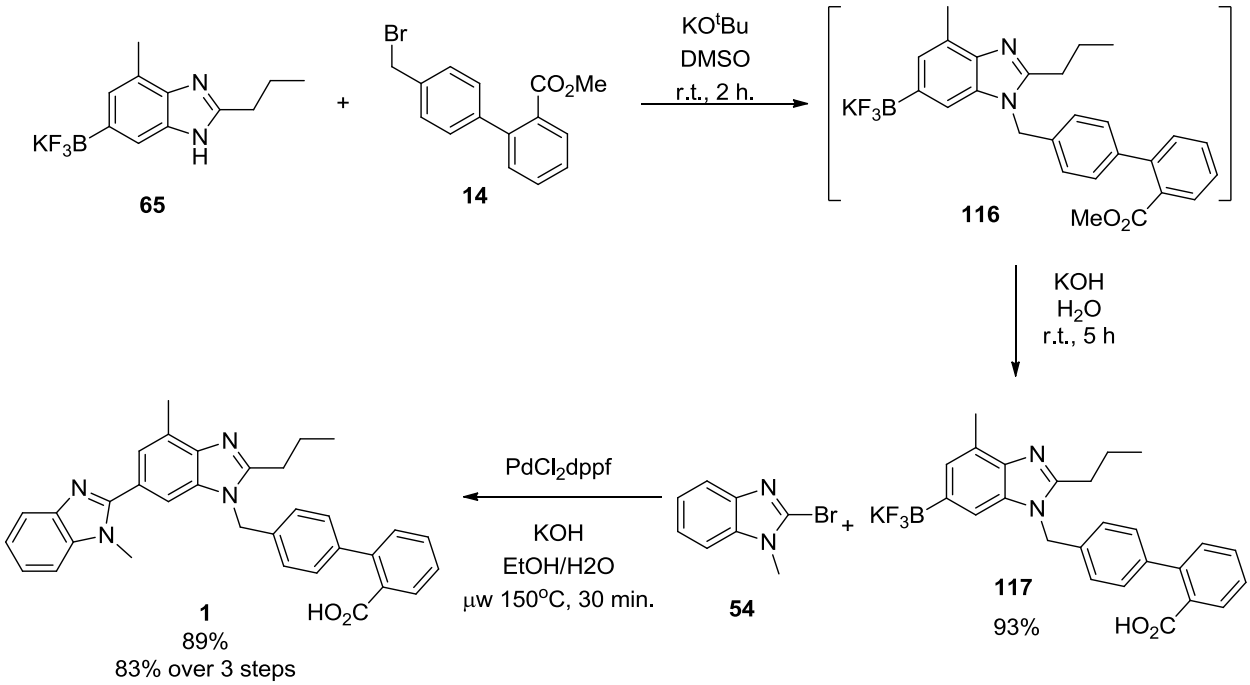


Figure 58. Second generation three-step preparation of telmisartan using biphenyl methyl ester

4.4.4 Palladium nanoparticles on graphene catalyzed Suzuki cross-coupling reaction to form telmisartan

In related work within the research group, palladium nanoparticles supported on graphene (Pd/G) have been developed in house.[67] This catalyst system demonstrates remarkable activity and recyclability in a wide range of Suzuki cross-coupling reactions. These nanoparticles have an average particle size of 7-9 nanometers (Figure 59) and in

some cases have reported turnover frequencies as high as 108,000 h^{-1} with a turnover number of 9000.

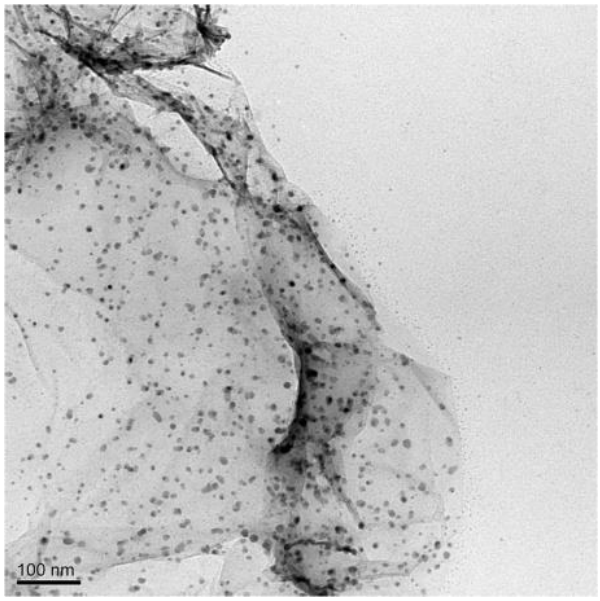
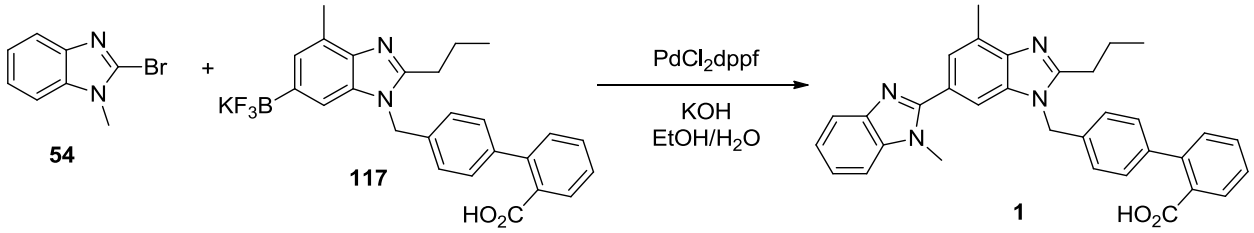


Figure 59. TEM of palladium nanoparticles on graphene

This catalyst system was evaluated for use in the key step of the telmisartan synthesis, in anticipation of conversion to a continuous process. Preliminary experiments using just 2 mol% of Pd/G led to a yield of 76% (Table 11, entry 1). In addition to the reasonable yield, the supported palladium nanoparticles demonstrated the ability to be recycled. After being removed from the initial reaction solution, the recovered catalyst successfully produced telmisartan in two subsequent reactions producing yields of 68% and 62%, respectively (entries 2 and 3). However, one problem associated with the use of the solid supported palladium nanoparticles is an increase in debromination of the starting material (**54**).

Table 11. Recycling experiments for palladium on graphene nanoparticles



entry	catalyst recycles	conditions	**1**
1	0	μw 150°C, 20 min	76
2	1	μw 150°C, 20 min	68
3	2	μw 150°C, 20 min	62

[a] **54** (0.19 mmol), **117** (0.20 mmol), 4 mL H_2O/EtOH (1:1 mixture). [b] Isolated yield

A common problem associated with the use of palladium catalyzed reactions for API synthesis, is the presence of small amounts of toxic metals contaminating the final product. One advantage to the use of palladium nanoparticles on a solid support is that the reaction mixture is heterogeneous, allowing for the catalyst to be removed by simple filtration which can minimize palladium content after purification. When compared to the isolated product from the homogeneous catalyst system ($PdCl_2$dppf), the Pd/G had a significantly lower amount of palladium. When analyzed by ICP the Pd/G only had 27 ppm of palladium in the final product (Table 12, entry 2). This value is almost four times lower than the 105 ppm of palladium in the product from the homogeneous system (entry 1).

Table 12. Palladium contamination comparison in telmisartan

entry	catalyst	Palladium content in product[a]
1	$PdCl_2$dppf	105 ppm
2	Pd/G	27 ppm

[a] Determined by ICP-OES.

CHAPTER V

CONTINUOUS PREPARATION OF TELMISARTAN

5.1 Background

With the goal of streamlining the total synthesis of telmisartan, an ideal scenario would be to eliminate the need for isolation of intermediates between reactions. The need for intermediate purification can greatly increase both waste and cost associated with a chemical process. Furthermore, adapting a chemical process to a continuous operation presents significant advantages to the traditional batch approach. However, additional considerations must be made when designing a continuous chemical strategy.

Continuous reactors have been used for a long time in industrial settings, but have only recently been utilized on a lab scale.[68] These flow reactors typically utilize small channels or tubing to perform more efficient chemical transformations. This elongated reaction space provides a large surface to volume ratio[69], allowing for improved heat transfer and component mixing throughout the reaction mixture.[70] These more efficient conditions provide lower variation in product purity when compared to conventional batch systems. Flow reactors also provide a more controlled environment for safer use of highly reactive materials or intermediates by reducing the amount of material being generated at a single point throughout the reaction.[71] Finally, flow systems provide a more straightforward progression to increase production. A single reactor could be run for a longer time or more reactors could be added and run in parallel.

Figure 60. Example of flow chemistry set-up

In order for a process to be a good potential candidate for flow chemistry there are a few additional aspects to be considered. The most important is the use of compatible components throughout the entire process, including the solvent system. Byproducts produced in the early stage should not interfere with the reactivity of downstream steps. Additionally, finding a single solvent or mixture of solvents that are compatible throughout the process eliminates the need for unnecessary solvent exchanges. In a similar manner, reaction conditions should be identified to perform the chemistry quickly and in high yield. Any unreacted starting materials can be carried forward, potentially leading to undesired byproducts or additional complications downstream. Finally, solubility throughout the system is a major concern. Precipitates or insoluble reactants could potentially clog the system causing significant problems and ultimately leading to the failure of the system. However, specific devices have been developed that can handle slurries and significant solid formation in flow, and some reactors provide a method to immobilize the insoluble components in a packed bed or similar system.

The batch process described in Chapter IV is an excellent candidate for continuous chemical processing. Starting from the synthons identified in the retrosynthetic analysis, all

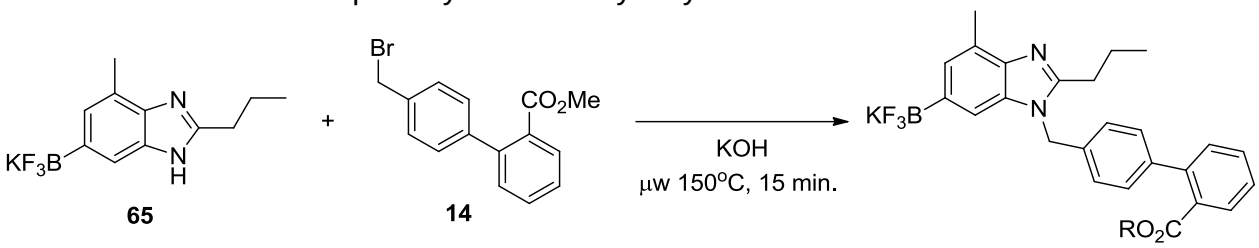
three transformations to form telmisartan are high yielding reactions, can be performed quickly or under mild conditions and all three are run under basic conditions. These three features make conversion to a continuous process very promising, but the batch process is not directly transferable to flow in its current state. Two major areas of consideration are compatible solvents and handling solids.

5.2 Development of continuous process for preparation of telmisartan

5.2.1 Solvent compatibility studies

The first aim in the transition from batch to flow is to find a new solvent system that is compatible with all three steps. Due to the need to run the reactions at elevated temperatures to facilitate quicker reaction times, solvents with high boiling points were explored. These solvents were also chosen for their reputation of having good solubility properties. The four solvents tested were DMSO, dimethylacetamide (DMA), dimethylformamide (DMF) and N-methylpyrrolidone (NMP). The first set of experiments ran were performing the alkylation and hydrolysis in one-pot using aqueous KOH as the base to facilitate the nucleophilic substitution and the saponification. The reactions were heated in a microwave and provided interesting results (Table 13). All four solvents provided good conversion to the carboxylic acid (**117**). DMSO and NMP showed the best conversion to desired product (entries 1 and 4) with 91% and 94%.

Table 13. One-pot alkylation and hydrolysis to form benzimidazole **117**



65 **14**

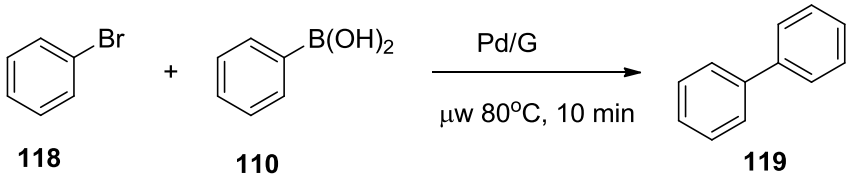
116 R=Me
117 R=H

entry[a]	solvent	117[b]	116[b]
1	DMSO	91	0
2	DMF	89	0
3	DMA	87	0
4	NMP	94	2

[a] **65** (100 mg, 0.36 mmol), **14** (109 mg, 0.36 mmol), KOH (100 mg, 1.8 mmol)
[b] Relative conversion determined by HPLC

The second round of experiments involved screening the compatibility of the Pd/G catalyst with the different solvents from above. In this case, it was found that the presence of water greatly increased the reactivity of the catalyst and that the presence of certain solvents greatly decreased the catalytic activity. A model Suzuki reaction between bromobenzene (**118**) and phenyl boronic acid (**110**) was used to test the activity of the catalyst in the four solvents mixed with water (Table 14). The DMA/H_2O system (entry 3) provided complete conversion to the desired biphenyl (**119**), however, the product was found to form a significant amount of precipitate which is not ideal for flow chemistry. The NMP reaction gave excellent conversion as well (entry 4), with a 94% conversion to the final product with no observable solid formation.

Table 14. Solvent compatibility study of Pd/G catalyst



118 **110** **119**

entry[a]	solvent	119[b]	precipitate formed
1	DMSO/EtOH/H2O	45	no
2	DMF/H2O	84	no
3	DMA/H2O	100	yes
4	NMP/H2O	94	no

[a] **118** (50 µL, 0.48 mmol), **110** (64 mg, 0.53 mmol), K_2CO_3 (198 mg, 1.4 mmol), Pd/G (2.5 mg, 2.4 µmol).
[b] Conversions determined by GC-MS.

5.2.2 Three-step one-pot preparation of telmisartan

Based on the preliminary experiments, NMP was chosen for its high reactivity in both systems and to avoid precipitate formation. With a solvent system targeted, the next aspect to be examined was the compatibility of all three steps with no isolation of intermediates. To test this concept, all three reactions were tested in a one-pot reaction using microwave heating to simulate flow conditions (Figure 61). This telescoped reaction sequence produced a 77% isolated yield of telmisartan without any major byproducts or problematic side reactions.

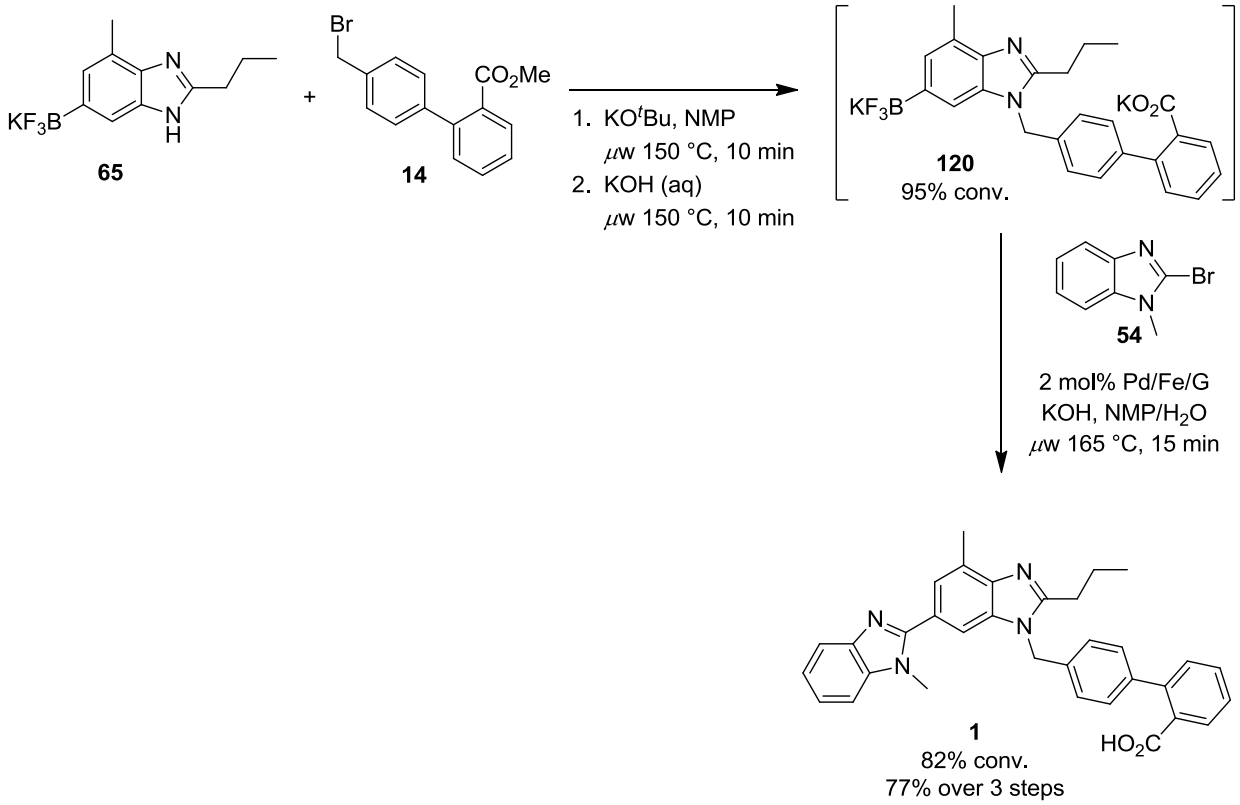


Figure 61. Three-step one-pot synthesis of telmisartan

*5.2.3 Continuous alkylation and hydrolysis to form benzimidazole **120***

The preliminary work ensured that all reagents and solvents are compatible throughout the process and would not interfere with downstream reactivity. These observations reinforced the notion that, with minor modifications, this synthetic approach to telmisartan is an ideal candidate for conversion to flow. First, the alkylation and de-esterification steps were performed in a Vapourtec E-series system with two 10 mL PFA reactor coils (Figure 62). In the first reaction stream, benzimidazole **65** was premixed with potassium *tert*-butoxide in NMP. This premixing allows for the deprotonation at the 1-position of the benzimidazole. This deprotonation serves two purposes: it improves the solubility of the trifluoroborate salt and helps to avoid the formation of unwanted Williamson ether byproducts.

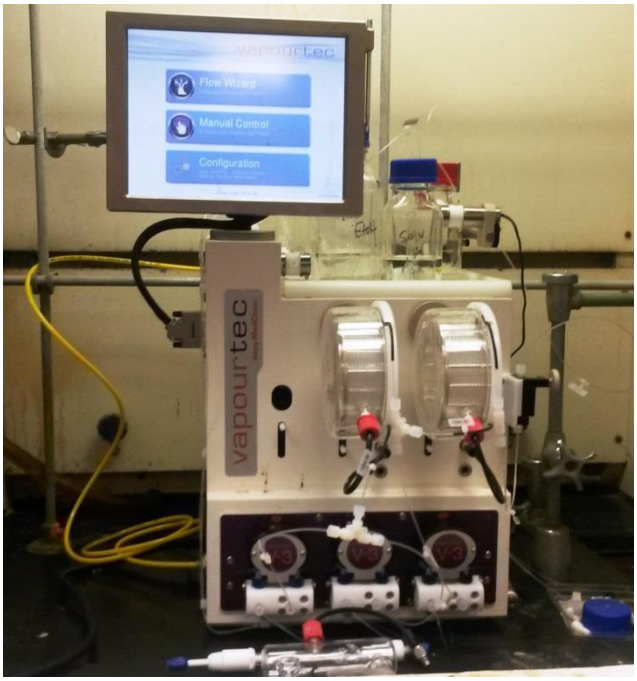


Figure 62. Vapourtec E-series

The second reaction stream contained a solution of bromide (**14**) in NMP. The solutions streams were mixed and fed into the first reactor coil. The first reactor coil was heated to 100^{o}C and required an estimated residence time of approximately 20 minutes. A molar excess of potassium hydroxide in water was added to the outlet from the first coil, which was then introduced into a second reactor 10 mL PFA reactor coil. This combined mixture was heated in the second coil at 120^{o}C with an estimated residence time of 10 minutes. The pressure of the entire system was maintained between 4 and 5 bar to prevent bubbles from forming within the reactor coils. These two chemical transformations yielded a conversion of 97% to the alkylated benzimidazole **120** (Figure 63).

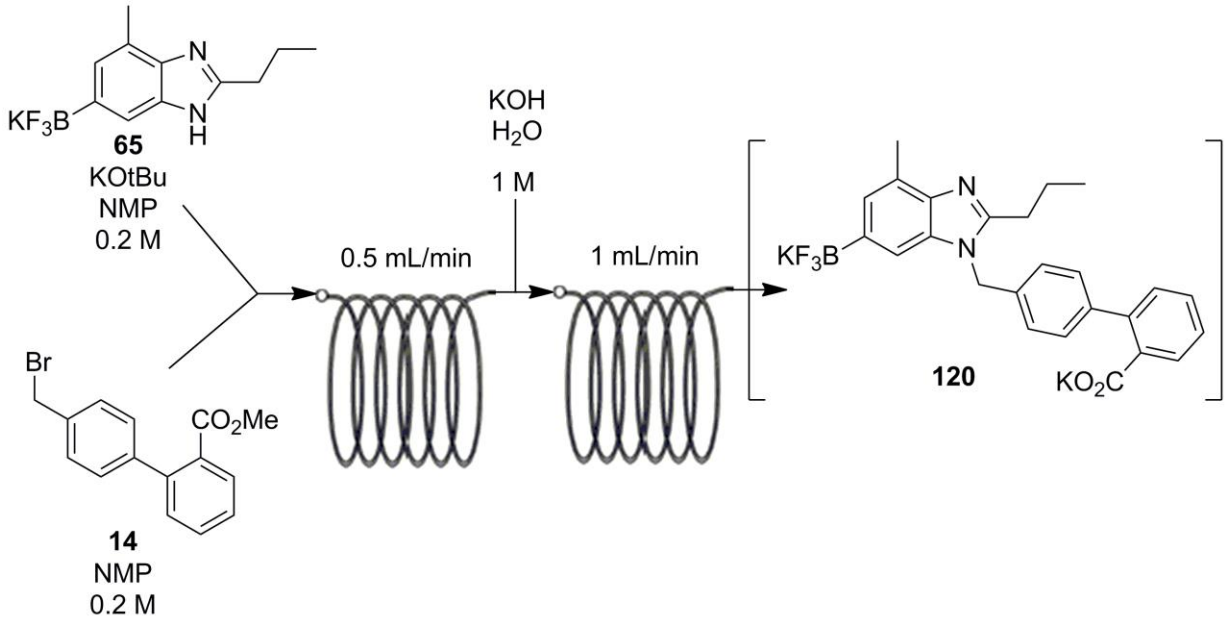


Figure 63. Flow schematic for alkylation and hydrolysis

5.2.4 Continuous Suzuki reaction to form telmisartan

With the first two continuous transformations complete, efforts were directed towards the development of continuous conditions for the Suzuki cross-coupling reaction. A commercially available silica supported palladium (Siliacat® DPP-Pd, Figure 64) was used to carry out the reaction. The catalyst has a diphenyl phosphine linked to the silica via a short alkyl chain and has a typical particle size from 60-150 μm. This catalyst was available in large enough quantities to allow for adequate experimentation and provided high conversions in test reactions completed under conventional microwave conditions.

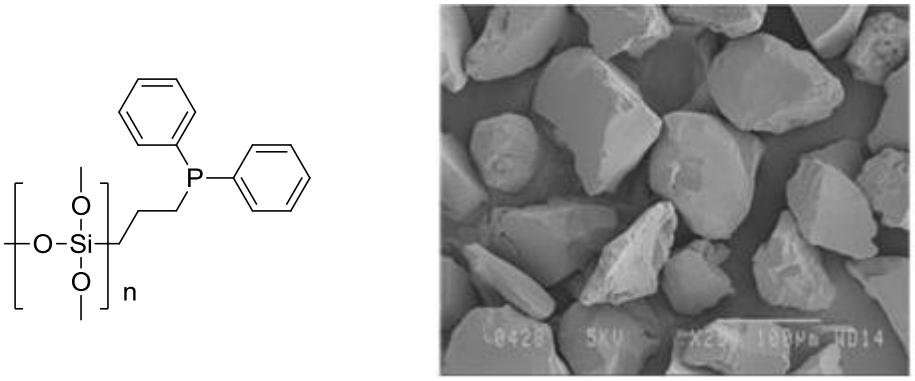


Figure 64. Ligand structure and TEM image of Siliacat® DPP-Pd catalyst

The Suzuki reaction was performed in a ThalesNano X-cube flow reactor (Figure 65). A packed bed of Siliacat® DPP-Pd was established by loading the catalyst into a cartridge fitted with frits at both ends. The outlet stream from the previous two steps was collected in a reservoir and then introduced to a solution containing 1.2 equivalents of 2-bromo-1-methylbenzimidazole (**54**) in a 1:1 NMP/H_2O solution. Optimized conditions were established when the catalyst bed was heated to 180^oC and the reaction mixture was passed through the column at a flow rate of 0.1 mL/min maintaining the pressure at 30-40 bar. The estimated residence time under these conditions was less than 5 min. When the final product was collected and isolated, this continuous process provided **1** with an overall yield of 86% over three chemical steps (Figure 66).

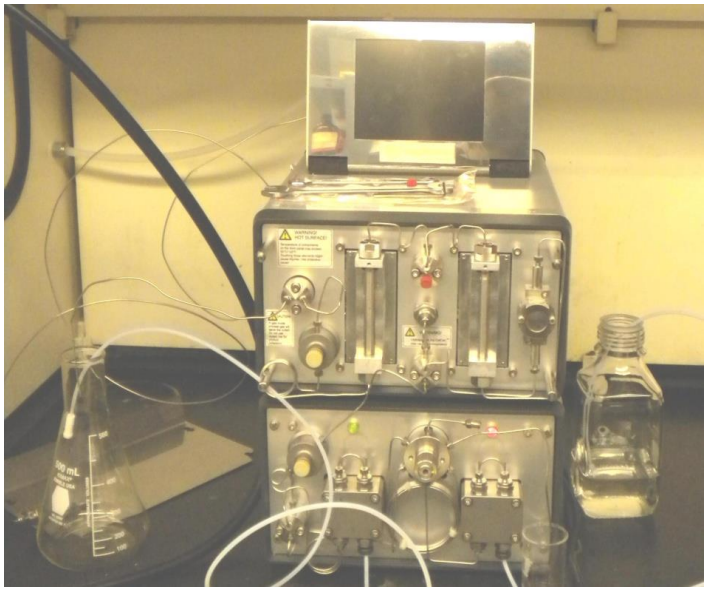


Figure 65. Thalesnano X-cube

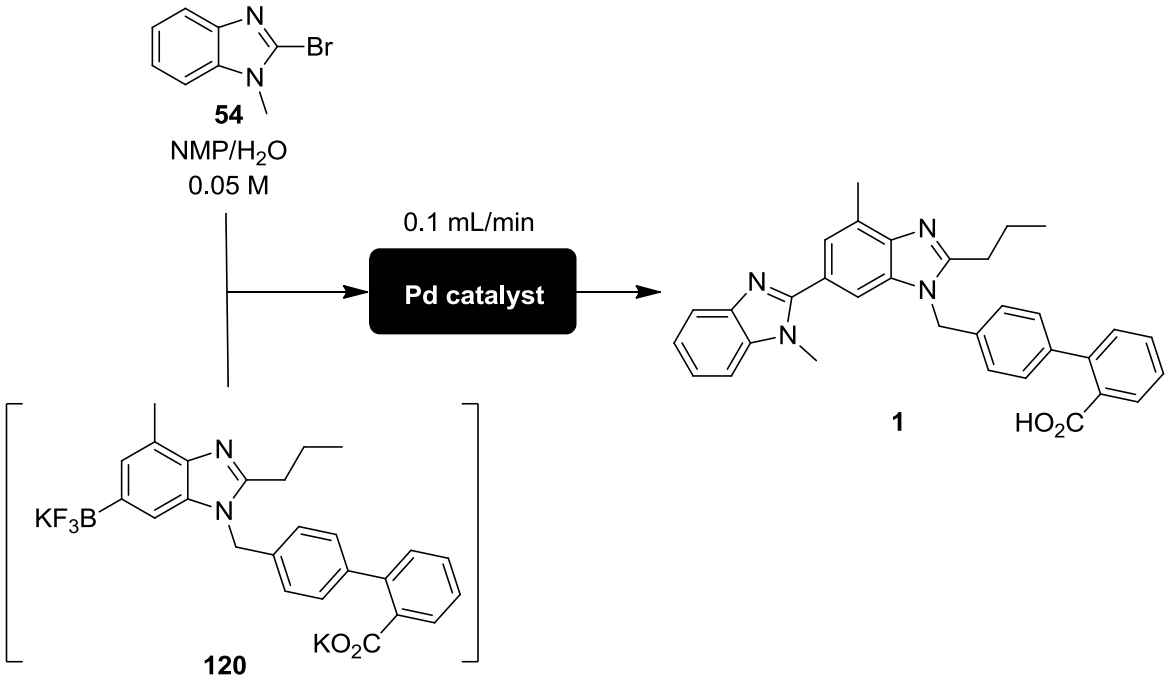


Figure 66. Flow schematic for Suzuki reaction to form telmisartan

This three step process marks the first flow-based synthesis of telmisartan to be reported in the literature[72] (Figure 67). It employs a highly efficient and convergent strategy that requires no intermediate purifications or solvent exchanges. The process features a Suzuki cross-coupling reaction catalyzed by a solid supported palladium catalyst in a packed column and produces an overall yield of 86% over three chemical steps. This continuous approach represents a significant improvement over existing methods that require numerous additional unit operations that add complexity and waste to the overall process. From a broader perspective, this flow-based method may serve as an example for the continuous preparation of other active pharmaceutical ingredients with similar structures.

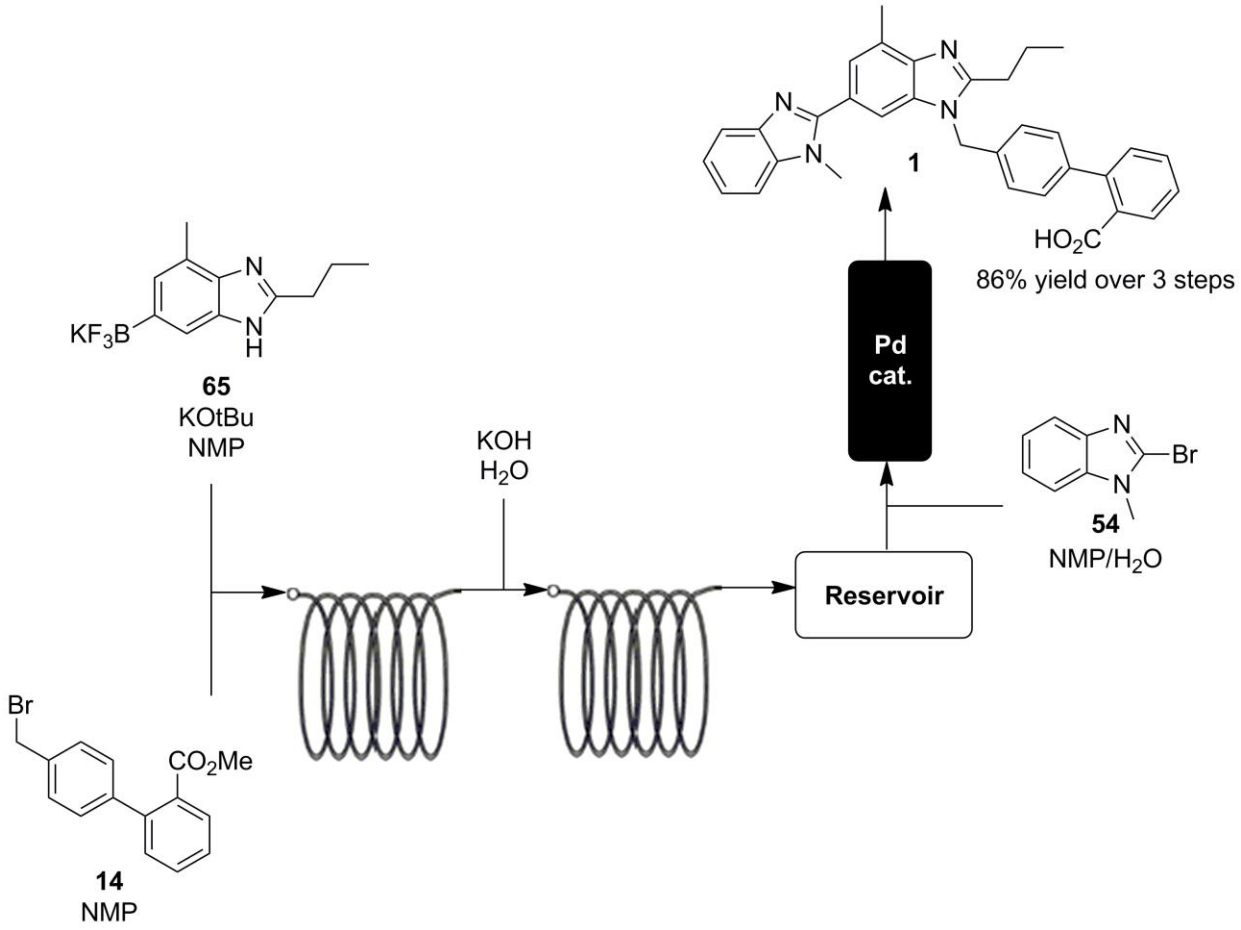


Figure 67. Flow schematic for three-step continuous preparation of telmisartan

CHAPTER VI

COMPARISON OF PROCESS OPTIONS

6.1 Process options overview

A direct and efficient preparation of telmisartan has been developed. This concise and convergent approach assembles the target molecule while featuring a Suzuki cross-coupling reaction to form a new carbon-carbon bond between two differentially functionalized benzimidazoles. This new strategy was enabled by the development of a regioselective bromination at the 2-position of 1-methylbenzimidazole (**55**). The overall approach has proceeded through various iterations, all based on the same synthetic approach. The first generation process (Figure 68) was designed in the most expeditious route possible to test the viability of the Suzuki reaction as a key step. Many improvements to this route were made in parallel with evaluation of the Suzuki cross-coupling reaction; these advances were incorporated into the second generation process. Despite being unoptimized, this first iteration provided telmisartan with a 29% overall yield, a slight improvement from the 21% reported originally in the Ries synthesis.

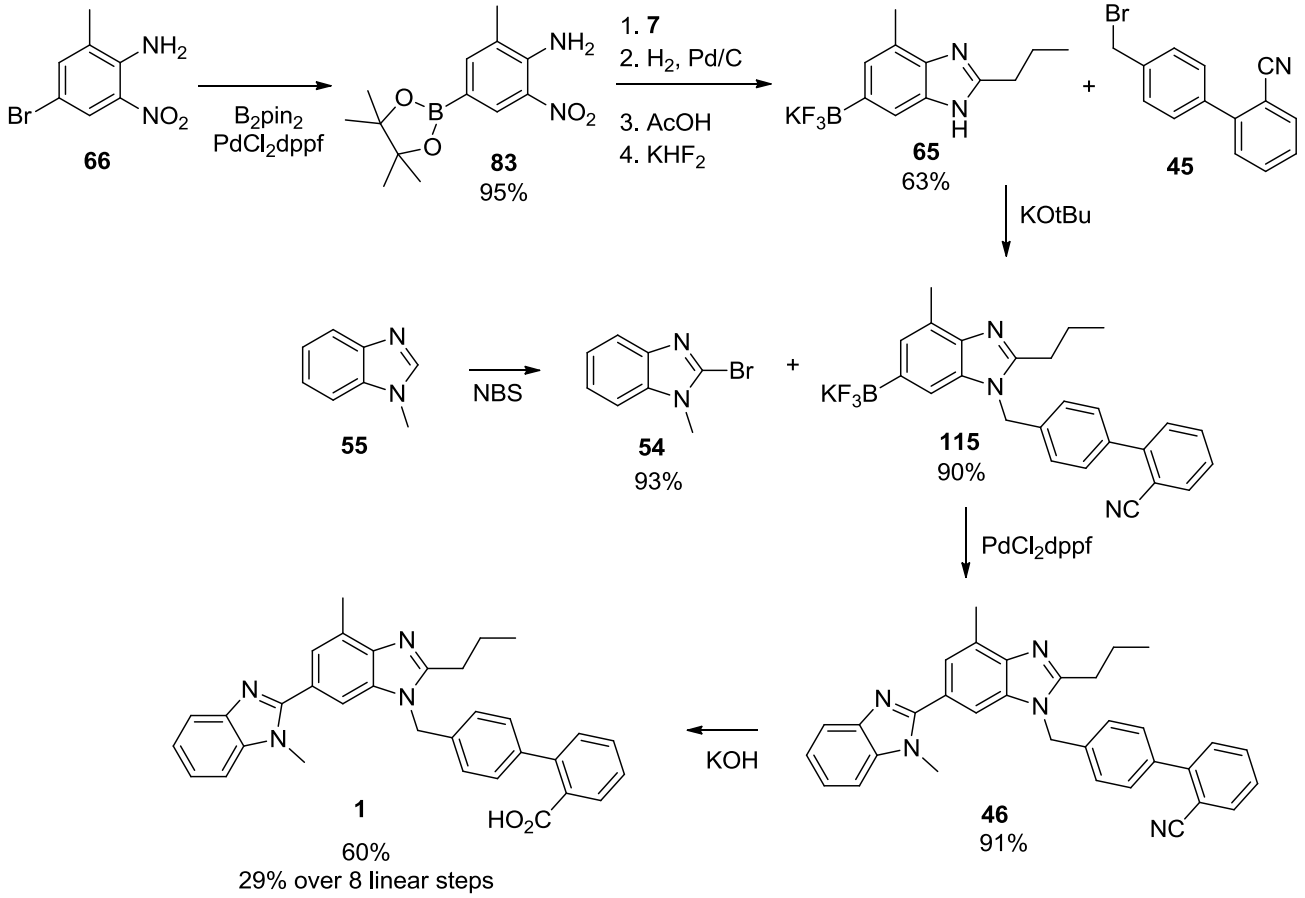


Figure 68. First generation synthesis of telmisartan

After the development of the first generation process, multiple aspects were identified as areas where significant improvements could be realized. The major areas targeted led to the development of an improved cyclization process for the central benzimidazole, a more efficient and atom economical installation of the trifluoroborate and finding a carboxylic acid derivative that could undergo an easy conversion to the final product. By addressing all three concerns, a much improved second generation process was achieved, featuring an improved cyclization, reduced palladium catalyst requirements, and a more atom economic boron source. This new process provides telmisartan with a high overall yield of 74% with two fewer unit operations (Figure 69).

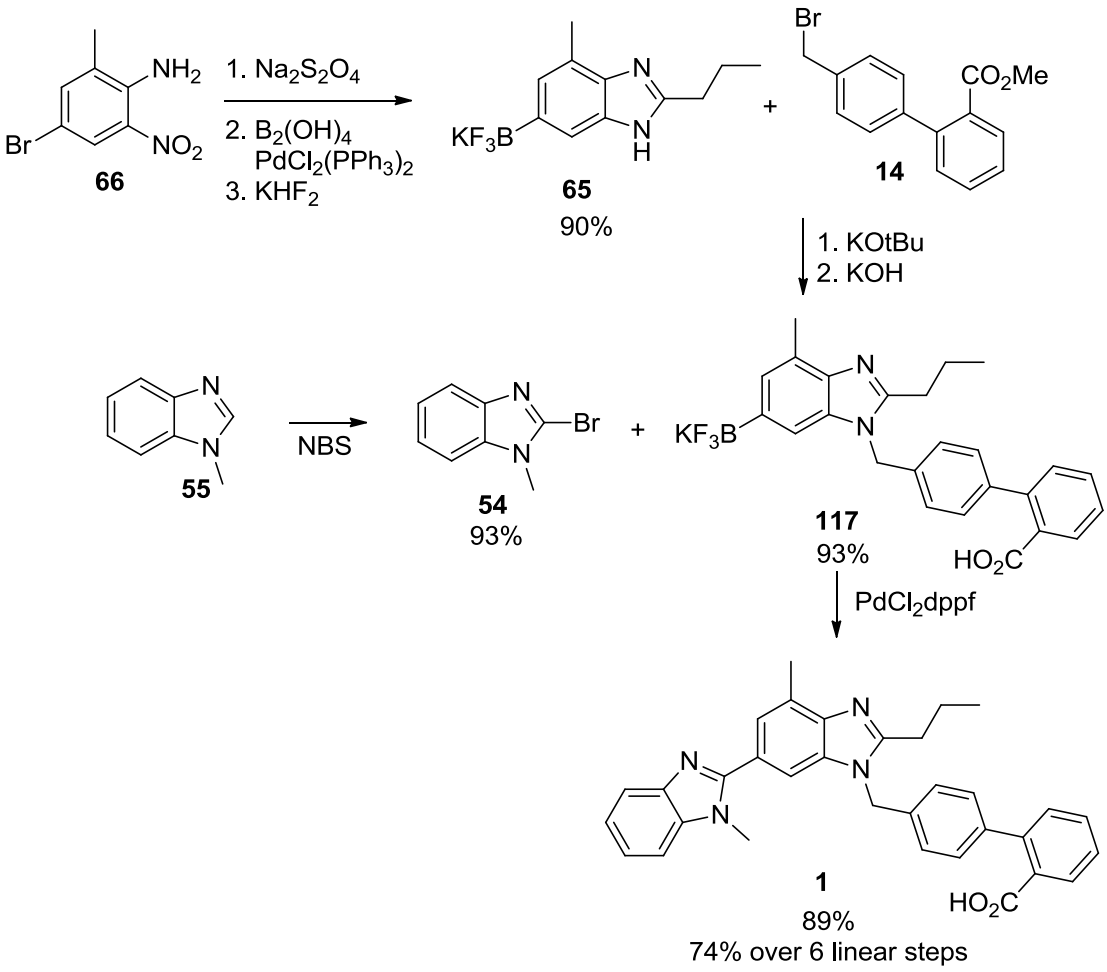


Figure 69. Second generation synthesis of telmisartan

Lastly, the final three steps were successfully converted to a continuous system in a similarly high-yielding process. After minor modifications of the second generation synthesis, conditions suitable for flow were established. The continuous synthesis of telmisartan was achieved by pumping advanced intermediates through two reactor coils and one packed bed column. This flow process is likely to offer significant improvements over the current commercial route, producing telmisartan with an 86% isolated yield and eliminating any need for purification of the intermediate compounds (Figure 70).

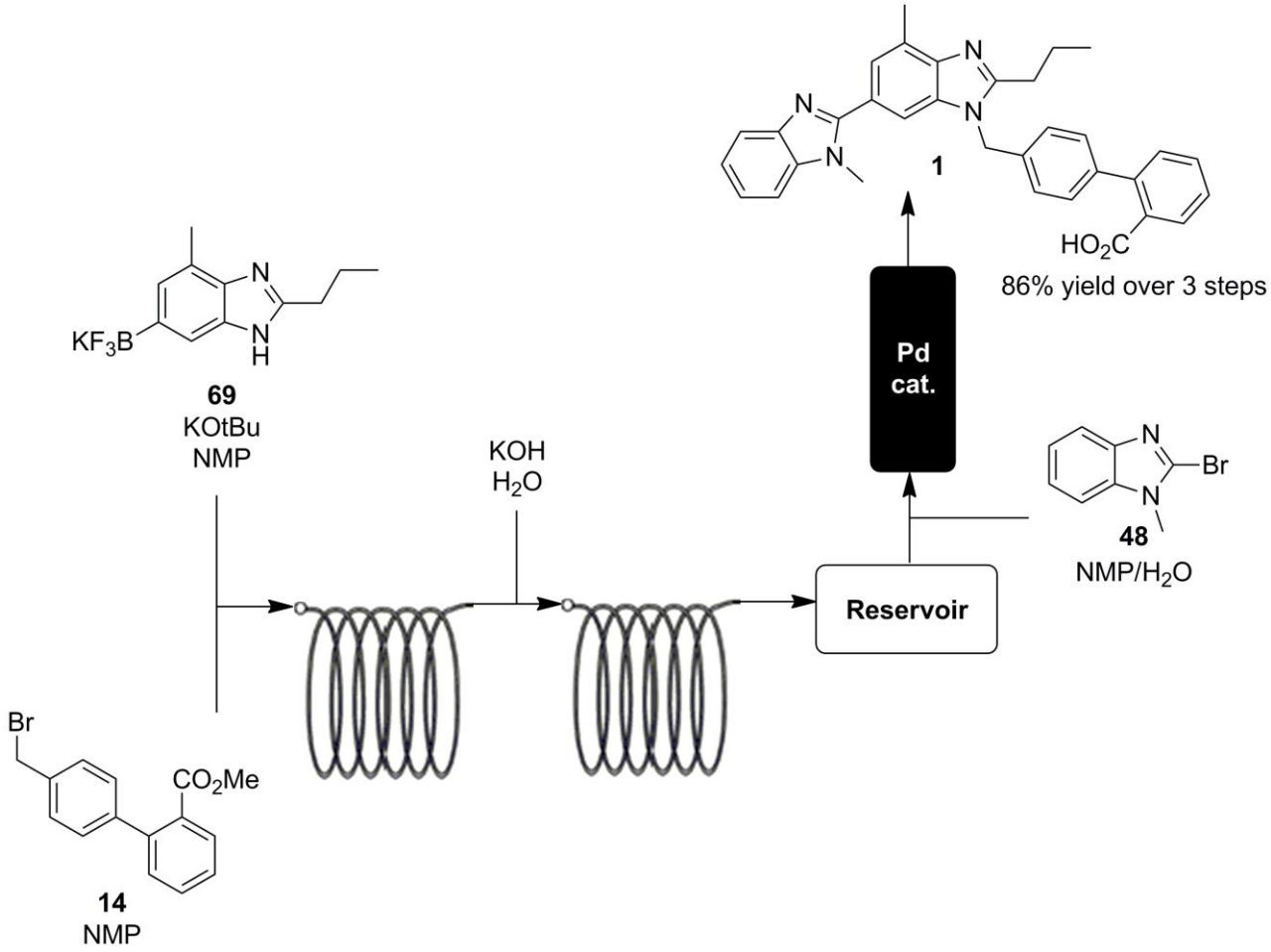
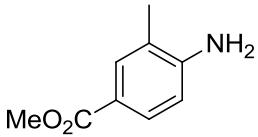
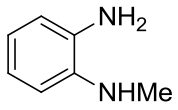
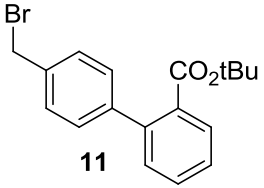
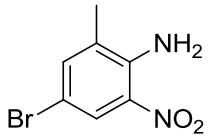
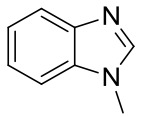
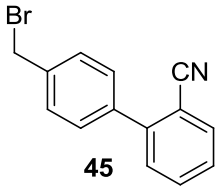
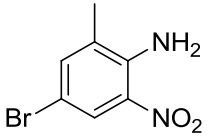
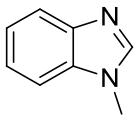
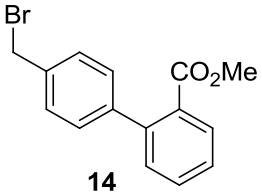
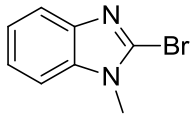
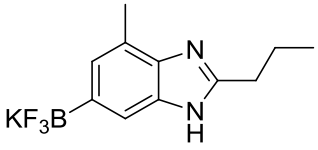
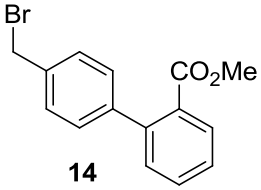


Figure 70. Flow preparation of telmisartan

When comparing this new approach with the original process, it is clear significant improvements have been made (Table 15). A sizable improvement in overall yield has been achieved while greatly decreasing the number of unit operations by eliminating the need for solvent exchanges and the isolation of intermediates.

Table 15. Telmisartan process comparisons

Entry	Process	Starting materials	Linear steps	Isolated intermediates	Overall yield
1	Original	 **6**  **9**  **11**	8	3	21%
2	First Generation	 **66**  **55**  **45**	8	4	29%
3	Second Generation	 **66**  **55**  **14**	6	2	74%
4	Flow	 **54**  **65**  **14**	3	0	86%

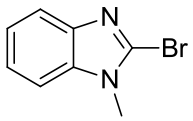
CHAPTER VII

EXPERIMENTAL

General Methods

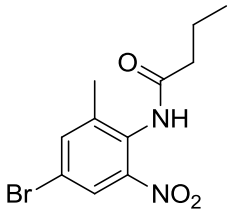
All reactions were carried out under ambient atmosphere, unless otherwise noted. Microwave reactions were performed using a CEM Discover SP microwave system. The reagents were purchased from commercial suppliers including Sigma Aldrich, Alfa Aesar, Fisher Scientific, TCI America or Matrix Scientific, and were used as received. Reactions were monitored using a Waters 2695 high-performance liquid chromatography equipped with a Waters 996 Photodiode Array Detector. GC-MS analyses were performed on Agilent 6890 gas chromatograph equipped with an Agilent 5973 mass selective detector. The ESI-Mass spectra were recorded on a Micromass Waters QTOF-2 mass spectrometer equipped with a custom built microspray source. Both ^{1}H and ^{13}C NMR Spectra were acquired on a Varian Mercury 300 MHz or a Bruker 400 MHz NMR spectrometer using DMSO-d_6 or $CDCl_3$ as solvents.

2-Bromo-1-methylbenzimidazole (54)



1-methylbenzimidazole (**55**, 5.0 g, 37.8 mmol) and *N*-bromosuccinimide (**62**, 20.2 g, 113.5 mmol) were taken up in 200 mL of THF. The solution was put under an atmosphere of nitrogen and heated at reflux for 1 h. The solvent was removed in rotary evaporator and the residue was taken up in 20 mL of MeOH. The solid remaining was filtered and discarded. 100 mL of EtOAc was added to the filtrate producing a white solid. The solid was filtered and dried providing 2-bromo-1-methylbenzimidazole (**54**, 7.4 g, 93%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 7.77 (d, 1H), 7.65 (d, 1H), 7.39 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 138.2, 135.4, 131.5, 124.8, 124.7, 117.0, 112.3, 33.0; HRMS (ESI-QTOF): *m/z* Calcd for $C_8H_7N_2Br + H^+$: 210.9871, found: 210.9862.

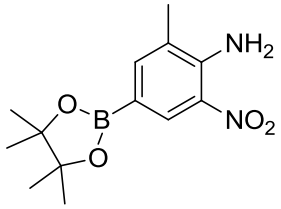
***N*-(4-bromo-2-methyl-6-nitrophenyl)butyramide (77)**



4-bromo-2-Methyl-6-nitroaniline **66** (1.0 g, 4.33 mmol) and butyryl chloride **7** (1.3 mL, 13.0 mmol) in 20 mL of ClBn were heated at 95^{o}C with a reflux condenser for 5 hours. After cooling to room temperature 80 mL of hexanes were added and a light yellow precipitate was formed. The precipitate was filtered and dried producing compound **77** (1.3 g, 82%). ^{1}H NMR (DMSO-d_6) δ 9.85 (s, 1 H), 7.95 (s, 1 H), 7.86 (s, 1 H), 2.3-2.2 (m, 5 H), 1.57 (m, 2 H),

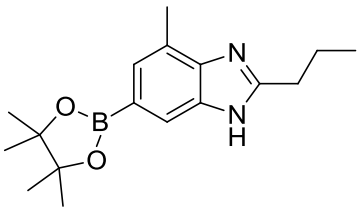
0.90 (t, 3 H); ^{13}C NMR (DMSO-d_6) δ 171.7, 147.4, 139.5, 137.5, 128.8, 125.0, 118.2, 37.6, 18.8, 18.0, 14.0.

(4-Amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (83).



4-bromo-2-methyl-6-nitroaniline **66** (5.0 g, 21.6 mmol) and bis(pinacolato)diboron **81** (10.1 g, 43.3 mmol) we placed in a 250 mL flask along with KOAc (6.4 g, 64.9 mmol) and $PdCl_2$dppf (1.5 g, 2.05 mmol). DMSO (50 mL) was added and the flask evacuated. The solution heated at 100°C for 5 h. The reaction mixture was cooled followed by the addition of 200 mL H_2O and extraction with EtOAc (3 x 100mL). The organic layer was combined and concentrated by rotary evaporation and the resulting oil was taken up in hexanes (200 mL). The precipitate that formed was filtered and discarded. The filtrate was evaporated and the residue was recrystallized in water, then dried to produce **83** (5.7 g, 95%). ^{1}H NMR (DMSO-d_6) δ 8.2 (s, 1H), 7.5 (s, 1H), 7.4 (s, 2H), 2.2 (s, 3H), 1.3 (s, 12H). ^{13}C NMR (DMSO-d_6) δ 147.1, 141.2, 131.5, 131.3, 126.4, 119.1, 84.3, 25.3, 18.4. ESI-MS: Calculated for $C_{13}H_{20}O_4N_2B^+$: 279.14, found: 279.15.

(4-Methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester (87)



Method A

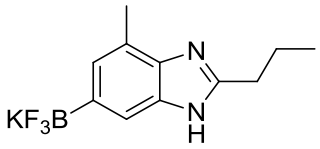
Butyryl chloride **7** (5.5 mL, 54 mmol) was added to a 250 mL flask containing 4-bromo-2-Methyl-6-nitroaniline **66** (5.0 g, 18 mmol) in Chlorobenzene (50 mL). The reaction mixture was stirred at 95°C for 5 h. The solvent was removed by rotary evaporation. The residue was taken up in methanol (50 mL) followed by the addition of 10 wt% Pd/C (1.0 g). The mixture was stirred at room temperature for 15 h under hydrogen balloon. After filtration through Celite, the filtrate was evaporated by rotary evaporation. The residue was taken up in acetic acid and refluxed for 1 h. The solvent was removed by rotary evaporation and the solid was rinsed with ethyl acetate producing (4-Methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester (**87**, 3.2 g, 60%) as a light brown solid. ^{1}H NMR (DMSO-d_6) δ 7.54 (s, 1 H), 7.22 (s, 1 H), 2.76 (t, 2 H), 2.43 (s, 3 H), 1.73 (m, 2 H), 1.23 (s, 12 H), 0.89 (t, 3 H); ^{13}C NMR (DMSO-d_6) δ 155.8, 128.5, 124.0, 118.7, 83.7, 30.7, 25.1, 21.4, 17.0, 14.1.

Method B

4-bromo-2-Methyl-6-nitrophenyl boronic acid pinacol ester (**83**) (2.0 g, 7.2 mmol) and butyraldehyde **41** (1.3 mL, 14.4 mmol) were added to a flask along with sodium dithionite (7.5 g, 43.2 mmol) and 40 mL of 50% MeOH in H_2O. The mixture was stirred at reflux for 5 h. The MeOH was removed by rotary evaporator. An additional 20 mL of H_2O was added to the remaining aqueous solution and was then extracted using DCM (3 x 50 mL). The

organic layer was removed by rotary evaporation. The resulting solid was rinse with ethyl acetate producing (4-Methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester (**87**) as a light brown solid (1.3 g, 60%).

Potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate (65).



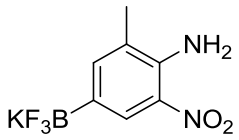
Method A

Butyryl chloride **7** (5.5 mL, 54 mmol) was added to a 250 mL flask containing 4-bromo-2-Methyl-6-nitroaniline **66** (5.0 g, 18 mmol) in Chlorobenzene (50 mL). The reaction mixture was stirred at 95°C for 5 h followed by evaporation. The residue was taken up in methanol (50 mL) followed by the addition of 10 wt% Pd/C (1.0 g). The mixture was stirred at room temperature for 15 h under hydrogen balloon. After filtration through Celite, the filtrate was evaporated. The residue was taken up in acetic acid and refluxed for 1 h. After removing the solvent by rotary evaporation, the residue was taken up in THF (100 mL) and combined with a solution of potassium bifluoride (7.0 g, 90 mmol) in H_2O (20 mL). The combined solution was stirred at room temperature for 5 h. Upon removal of THF, the precipitate was filtered and rinsed using EtOAc, yielding **65** as a white solid (3.9 g, 63%). ^{1}H NMR (DMSO-d_6) δ 7.2 (s, 1H), 7.1 (s, 1H), 2.8 (t, 2H), 2.5 (s, 3H), 1.7 (m, 2H), 0.9 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 152.5, 130.7, 129.3, 121.4, 113.0, 28.5, 21.0, 17.1, 14.0. ESI-MS: Calculated for $C_{11}H_{14}N_2BF_3K^+$: 281.08, found: 281.07.

Method B

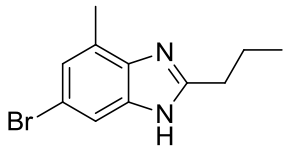
4-bromo-2-Methyl-6-nitroaniline (**66**) (2.0 g, 8.7 mmol) and butyraldehyde **41** (1.6 mL, 17.3 mmol) were added to a flask along with sodium dithionite (7.5 g, 43.2 mmol) and 40 mL of 50% MeOH in H_2O. The mixture was stirred at reflux for 5 h. The MeOH was removed by rotary evaporator. An additional 20 mL of H_2O was added to the remaining aqueous solution and was then extracted using DCM (3 x 50 mL). The organic layer was concentrated by rotary evaporator and then taken up in 80 mL of EtOH. The solution was added to a flask containing diboronic acid (2.3 g, 26.0 mmol), KOAc (2.5 g, 26.0 mmol), $PdCl_2(PPh_3)_2$ (182 mg, 0.26 mmol) and triphenylphosphine (91 mg, 0.35 mmol). The flask was then evacuated and placed under nitrogen. The solution was heated at 75 °C for 10 h. The reaction mixture was cooled, filtered and then concentrated by rotary evaporator followed by the addition of 80 mL of H_2O. The aqueous mixture was then extracted with EtOAc (3 x 100 mL). The organic layer was combined, concentrated and then the volume was adjusted to 100 mL by adding more EtOAc. The solution was then combined with a solution of potassium bifluoride (3.4 g, 43.3 mmol) in H_2O. The biphasic mixture was stirred at room temperature for 5 hours. The precipitate was filtered, rinsed using THF and then dried, yielding potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate (**65**) as a white solid (2.2 g, 90%).

Potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate (88).



4-bromo-2-Methyl-6-nitroaniline **66** (1.0 g, 4.3 mmol) was taken up in 20 mL of THF and added to a solution of potassium bifluoride (1.7 g, 21.6 mmol) in 5 mL H_2O. The combined solutions were stirred at room temperature for 5 h. Upon removal of THF, the precipitate was filtered and rinsed using ethyl acetate. Potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate (88) was produced as an orange solid (1.0 g, 93%). ^{1}H NMR (DMSO-d_6) δ 7.81 (s, 1 H), 7.31, (s, 1 H), 6.78 (s, 2 H), 2.15 (s, 3 H). ^{13}C NMR (DMSO-d_6) δ 143.2, 141.4, 131.2, 125.6, 123.8, 18.3.

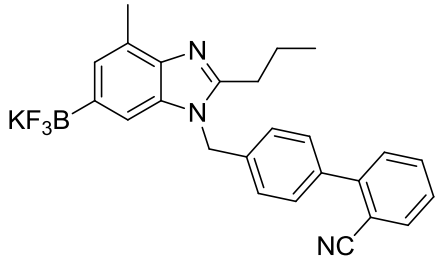
6-Bromo-4-methyl-2-propylbenzimidazole (95).



Butyraldehyde **41** (3.1 mL, 34.6 mmol) was added to a 250 mL flask containing 4-bromo-2-methyl-6-nitroaniline **66** (4.0 g, 17.3 mmol) and sodium dithionite (18.1 g, 103.9 mmol) in 80 mL of 50% MeOH in H_2O. The reaction was stirred at reflux for 5 h. The methanol was removed via rotary evaporator. To the remaining aqueous solution, an additional 40 mL of water was added and the mixture was extracted using EtOAc (3 x 80 mL). The organic layer was dried using magnesium sulfate. After filtration, the organic layer was removed via rotary evaporator and the resulting solid was dried in the oven producing 6-Bromo-4-methyl-2-propylbenzimidazole **95** as a white solid (4.3 g, 97%). ^{1}H NMR

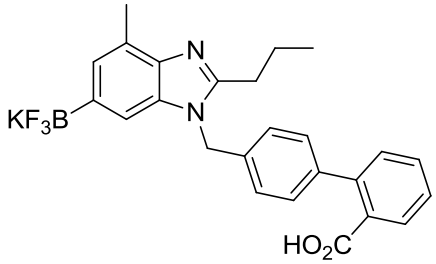
(DMSO-d_6) δ 7.47 (s, 1H), 7.08 (s, 1H), 2.77 (t, 2H), 2.47 (s, 3H), 1.79 (m, 2H), 0.95 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 155.7,124.0, 113.1, 30.5, 20.9, 16.4, 13.6; HRMS (ESI-QTOF): *m/z* Calcd for $C_{11}H_{13}N_2Br + H^+$: 253.0340, found: 253.0323.

Potassium (1-((2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propylbenz-imidazol -6-yl) trifluoroborate (115)



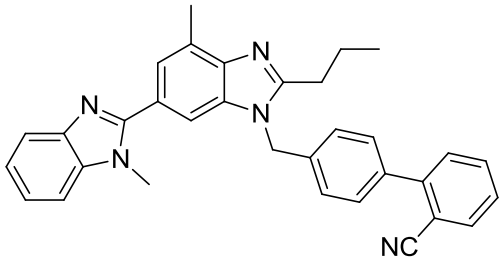
Potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate **65** (1.0 g, 3.6 mmol) was added to a solution of KO*t*Bu (1.2 g, 10.7 mmol) in DMSO (20 mL) and stirred for 30 min at room temperature. 4'-(bromomethyl)-[1,1'-biphenyl]-2-carbonitrile **45** (1.0 g, 3.7 mmol) was then added to the reaction mixture and stirred for 2 h at room temperature. H_2O (80 mL) was then added to the reaction mixture producing a white precipitate. The precipitated material was filtered, rinsed with THF and then dried, producing potassium (1-((2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propylbenz-imidazol -6-yl) trifluoroborate **115** as a white solid (1.5 g, 91% yield). ^{1}H NMR (DMSO-d_6) δ 7.9-7.1 (m, 10 H), 5.55 (s, 2 H), 2.83 (t, 2 H), 2.49 (s, 3 H), 1.75 (m, 2 H), 0.94 (t, 3 H). ^{13}C NMR (DMSO-d_6) δ 155.4, 144.4, 143.9, 138.4, 137.4, 135.1, 134.3, 134.0, 130.6, 129.6, 128.7, 127.0, 119.0, 114.0, 110.6, 46.1, 29.1, 21.2, 17.0, 14.3.

Potassium(1-(2'-carboxy-[1,1'-biphenyl]-4-yl)-4-methyl-2-propyl-benzimidazole-6-yl) trifluoroborate (117)



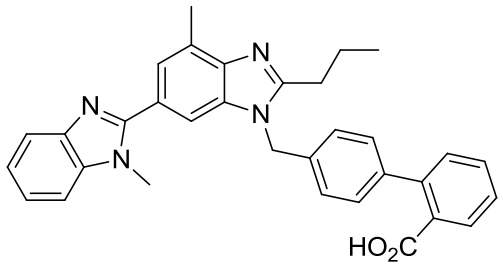
Potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate **65** (2.0 g, 7.1 mmol) was added to a solution of KO*t*Bu (2.4 g, 21 mmol) in DMSO (20 mL) and stirred for 30 min at room temperature. 4'-Bromomethyl-[1,1'-biphenyl]-methyl ester **14** (2.2 g, 7.1 mmol) was then added to the reaction mixture and stirred for 2 h at room temperature. A solution of 2 g KOH (35 mmol) in H_2O (80 mL) was then added to the reaction mixture and stirred for an additional 5 h at room temperature. The solution was adjusted to pH 4 using AcOH, producing a white precipitate. The precipitated material was filtered, rinsed with THF and then dried, yielding potassium (1-(2'-carboxy-[1,1'-biphenyl]-4-yl)-4-methyl-2-propyl-benzimidazole-6-yl) trifluoro-borate (**117**) as a white solid (3.2 g, 93% yield). ^{1}H NMR (DMSO-d_6) δ 7.22-7.72 (m, 10H), 5.80 (s, 2H), 3.19 (t, 2H), 2.54 (s, 3H), 1.76 (m, 2H), 0.96 (t, 3H); ^{13}C NMR (DMSO-d_6) δ 170.2, 152.8, 141.2, 141.0, 134.8, 132.2, 131.6, 131.2, 129.8, 129.5, 129.4, 128.1, 126.9, 122.2, 112.1, 47.4, 27.3, 21.5, 17.1, 14.1; HRMS (ESI-QTOF): *m/z* Calcd for $C_{25}H_{23}O_2N_2BF_3K + H^+$: 491.1520, found: 491.1513.

4’-((1,7’-Dimethyl-2’-propyl-[2,5’-dibenzimidazol]-1’-yl) methyl)-[1,1’-biphenyl]-2-carbo-nitrile (46).



2-Bromo-1-methylbenzimidazole (**54**, 50 mg, 0.24 mmol) and potassium (1-((2’-cyano-[1,1’-biphenyl]-4-yl)methyl)-4-methyl-2-propylbenz-imidazol -6-yl) trifluoroborate (**115**,123 mg, 0.26 mmol) were combined with KOH (39.9 mg, 0.71 mmol) and 5 mol% $PdCl_2$dppf (8.7 mg, 0.012 mmol) in a 1:1 mixture of THF and MeOH (4 mL). The mixture was heated at 120^{o}C, in a sealed tube, by microwave irradiation for 10 minutes. The solution was filtered through Celite and then 12 mL of H_2O was added. The resulting precipitate was filtered and dried in oven producing 4’-((1,7’-dimethyl-2’-propyl-[2,5’-dibenzimidazol]-1’-yl) methyl)-[1,1’-biphenyl]-2-carbo-nitrile (#) (106 mg, 91%). ^{1}H NMR (DMSO-d_6) δ 7.9-7.1 (m, 14 H), 5.67 (s, 2 H), 3.80 (s, 3 H), 2.90 (t, 2 H), 2.61 (s, 3 H), 1.80 (m, 2 H), 0.97 (t, 3 H).

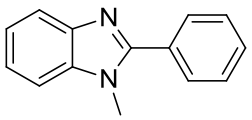
Telmisartan (1).



2-bromo-1-methyl-benzimidazole (**54**, 40 mg, 0.19 mmol) and Potassium(1-(2'-carboxy-[1,1'-biphenyl]-4-yl)-4-methyl-2-propyl-benzimidazole-6-yl) trifluoroborate (**117**) (97.6 mg, 0.20 mmol) were combined with KOH (31.9 mg, 0.57 mmol) and 2 mol% $PdCl_2$dppf (2.8 mg, 0.004 mmol) in a 1:1 mixture of H_2O and EtOH (4 mL). The solution was heated using microwave irradiation, in a sealed tube, with stirring for 30 minutes at 150°C. Temperature was monitored using an IR temperature sensor. The solution was filtered through Celite. To the filtrate, 10 mL of H_2O was added and the pH was adjusted to 4 using AcOH. The resulting precipitate was filtered and dried in oven producing telmisartan (86.7mg, 89% yield). ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1H), 8.04 (d, 1H), 7.00-7.52 (m, 12H), 5.43(s, 2H), 3.76 (s, 3H), 3.16 (t, 2H), 2.73 (s, 2H), 2.02 (m, 2H), 1.18 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 158.2, 155.7, 145.2, 144.5, 143.3, 142.7, 137.2, 136.2, 135.6, 135.3, 132.1, 131.9, 131.0, 130.6, 130.4, 129.0, 128.8, 125.2, 124.9, 124.8, 123.5, 121.4, 113.0, 111.0, 50.5, 33.5, 31.7, 24.1, 18.6, 15.8; HRMS (ESI-QTOF): *m/z* Calcd for $C_{33}H_{30}O_2N_4$ + H^+: 515.2447, found: 515.2468.

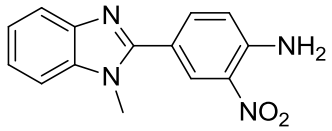
Proof of Concept Suzuki Reactions with 2-Bromo-1-methylbenzimidazole

*1-Methyl-2-phenylbenzimidazole (**111**)*



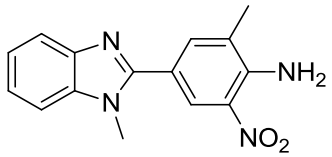
2-bromo-1-methylbenzimidazole **54** (50 mg, 0.24 mmol) and phenyl boronic acid **110** (31.8 g, 0.26 mmol) were combined in a CEM microwave test tube. To the tube triethylamine (100 µL, 0.71 mmol), palladium acetate (2.7 mg, 12 µmol) and triphenyl phosphine (9.3 mg, 36 µmol) were added. Finally, 4 mL of DMF was added the mixture was heated under microwave irradiation for 10 min at 150^{o}C. The reaction was monitored by HPLC and produced a 98% relative conversion to **111**. Product was confirmed by mass, but was not isolated or characterized further.

*2-(4-amino-3-nitrophenyl)-1-methylbenzimidazole (**113**)*



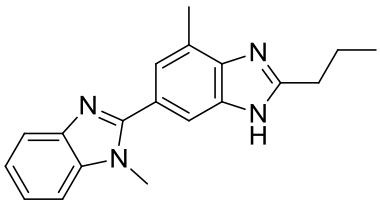
2-bromo-1-methylbenzimidazole **54** (50 mg, 0.24 mmol) and 4-amino-3-nitrophenyl boronic acid pinacol ester **112** (68.8 g, 0.26 mmol) were combined in a CEM microwave test tube. To the tube triethylamine (100 µL, 0.71 mmol), palladium acetate (2.7 mg, 12 µmol) and triphenyl phosphine (9.3 mg, 36 µmol) were added. Finally, 4 mL of DMF was added the mixture was heated under microwave irradiation for 10 min at 150^{o}C. The reaction was monitored by HPLC and produced a 90% relative conversion to **113**. Product was confirmed by mass, but was not isolated or characterized further.

*2-(4-amino-3-methyl-5-nitrophenyl)-1-methylbenzimidazole (**40**)*



2-bromo-1-methylbenzimidazole **54** (50 mg, 0.24 mmol) and 4-amino-3-methyl-5-nitrophenyl boronic acid pinacol ester **83** (72.5 g, 0.26 mmol) were combined in a CEM microwave test tube. To the tube KOH (39.9 mg, 0.71 mmol), palladium acetate (2.7 mg, 12 µmol) and triphenyl phosphine (9.3 mg, 36 µmol) were added. Finally, 4 mL of a 1:1 mixture of ACN and MeOH was added and the mixture was heated under microwave irradiation for 20 min at 150^{o}C. The reaction was monitored by HPLC and produced a 80% relative conversion to **40**. Product was confirmed by mass, but was not isolated or characterized further.

*1,7'-dimethyl-2'-propyl-2,6'-dibenzimidzaole (**10**)*



2-bromo-1-methylbenzimidazole **54** (50 mg, 0.24 mmol) and (4-methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester **87** (122.8 g, 0.26 mmol) were combined in a CEM microwave test tube. To the tube KOH (39.9 mg, 0.71 mmol), palladium acetate (2.7 mg, 12 µmol) and triphenyl phosphine (9.3 mg, 36 µmol) were added. Finally, 4 mL of MeOH was added and the mixture was heated under microwave irradiation for 20 min at 150^{o}C. The reaction was monitored by HPLC and produced a 46% relative conversion to **10**. Product was confirmed by mass, and matched premade standard.

Procedure for Suzuki cross coupling reaction using Pd/G and recycling the heterogeneous catalyst.

2-bromo-1-methyl-benzimidazole (**54**, 20 mg, 0.094 mmol) was dissolved in a mixture of 2 mL H_2O:EtOH (1:1) and placed in a 10 mL microwave tube. To this was added **117** (48.8 mg, 0.099 mmol), and potassium hydroxide (21.3mg, 0.38 mmol). The palladium on graphene catalyst (Pd/G) (2.5 mg, 1.9 µmol) was then added, and the tube was sealed and heated under microwave irradiation (250 W, 2.45 MHz) at 150 °C for 20 minutes. Upon the completion of the reaction period, the reaction mixture was diluted with 2 mL of 10 mg/mL KOH in EtOH and centrifuged to remove the solid catalyst. The EtOH/KOH washing were repeated twice to ensure the complete dissolution of the product from the surface of the catalyst. The solution was decanted and the solvent was partially concentrated in *vacuo*. After adjusting the pH of the remaining solution to 4 using AcOH, the precipitated telmisartan product was isolated by filtration and dried in the oven (76% isolated yield). In case of recycling the Pd/G nanoparticles, the solid catalyst was removed by centrifugation and added to the next reaction mixture using fresh reagents as indicated above. The reaction solution was heated in the microwave at 150 °C for 20 minutes and the same purification was applied, affording telmisartan with an isolated yield of 68% and 62% in the second and third reactions, respectively.

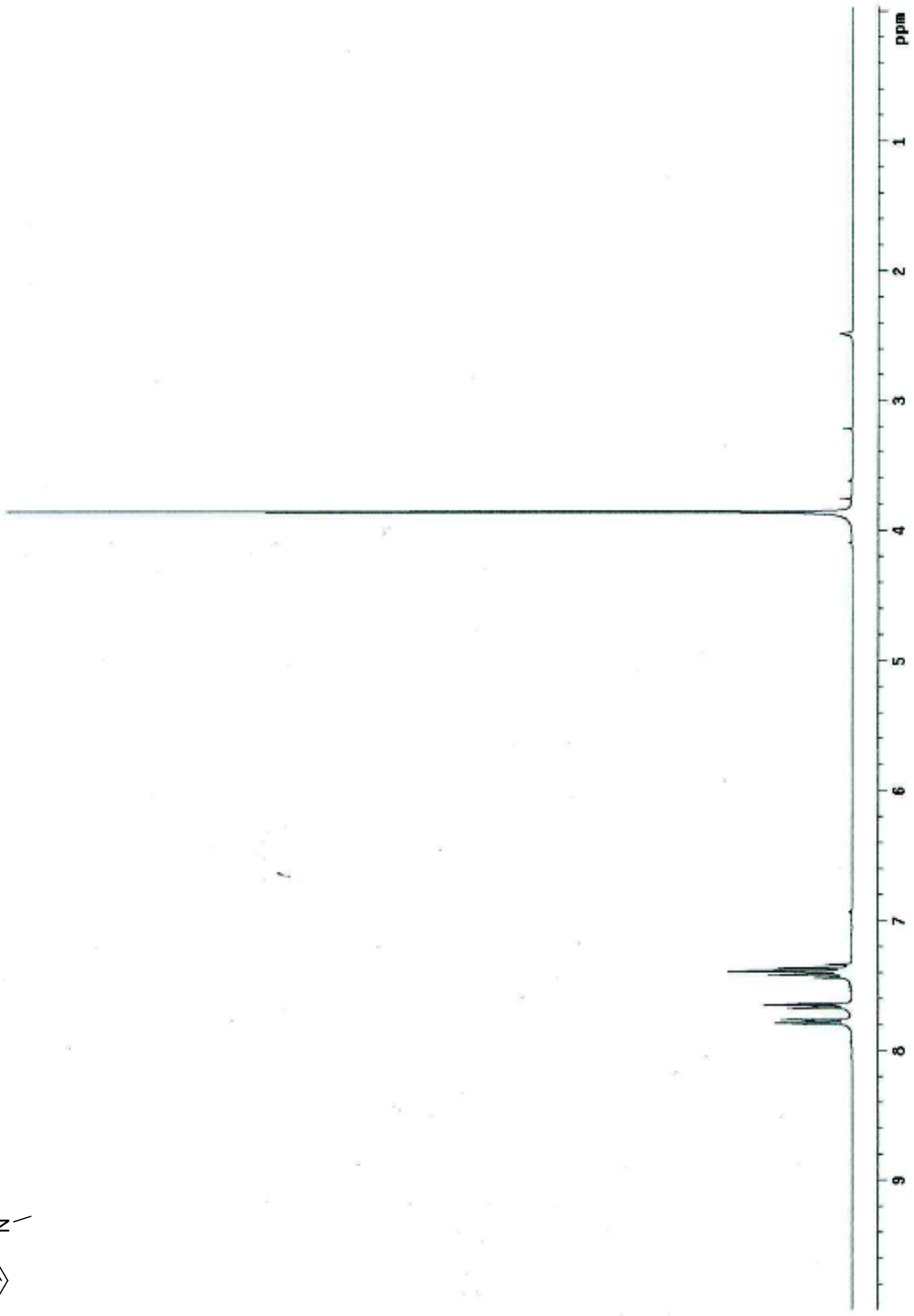
Procedure for Flow Reactions.

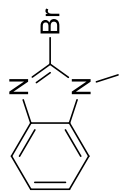
A mixture of **3** (1 equiv., 0.2 M) and KOtBu (3 equiv.) in NMP was stirred in the first inlet reservoir. A second inlet solution containing **4** (1 equiv., 0.2 M) in NMP was prepared, and each were pumped at 0.25 mL/min through a T-joint into a Vapourtec E-series. The reaction mixture was flowed through a 10 mL reactor coil at 100°C. Directly after the first coil, a third pump introduced a third solution containing aqueous KOH (10 equiv., 1 M) at

0.5 mL/min. The combined stream was pumped into a second 10 mL reactor coil at 120°C. The outlet was collected in a reservoir then combined with a fourth solution containing bromobenzimidazole **6** (1.2 equiv., 0.05 M) in a 50/50 mixture of NMP/H_2O. This combined stream was then pumped into a ThalesNano X-cube at 0.1 mL/min through two cartridges containing 100 mg of catalyst (SiliaCat® DPP-Pd) kept at 180°C. The final outlet was collected (2 mL, 20 min) and diluted 4x with H_2O and acidified using AcOH. The resulting precipitate was filtered and stirred in chloroform. The remaining solid was discarded and the chloroform was removed by rotary evaporator. The residue was taken up in a dilute aqueous KOH solution and acidified using AcOH. The precipitate was filtered and dried to produce **1** (20.7 mg, 81% yield, 97% purity by HPLC).

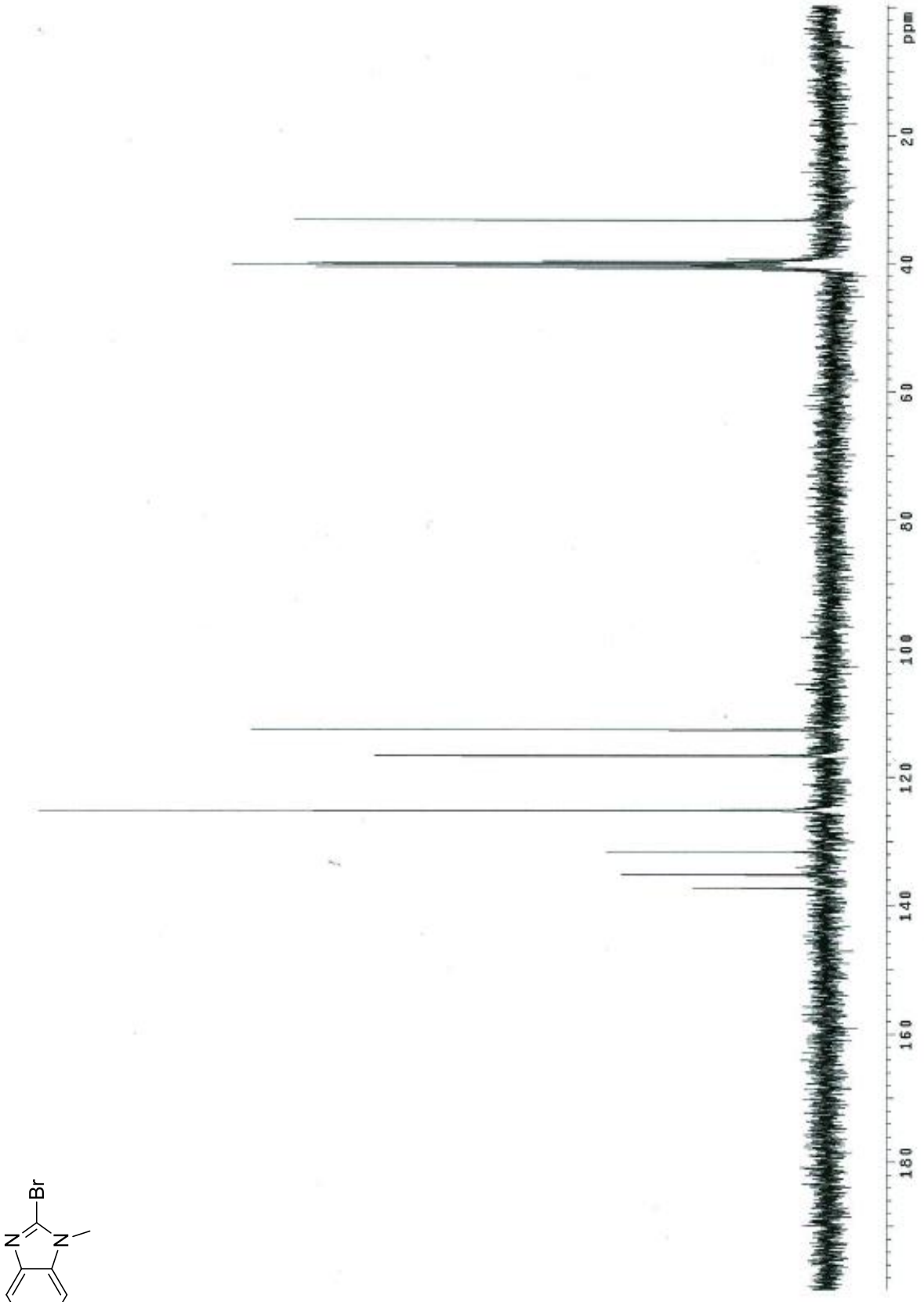
APPENDICES

^{1}H NMR: 2-Bromo-1-methylbenzimidazole (54)

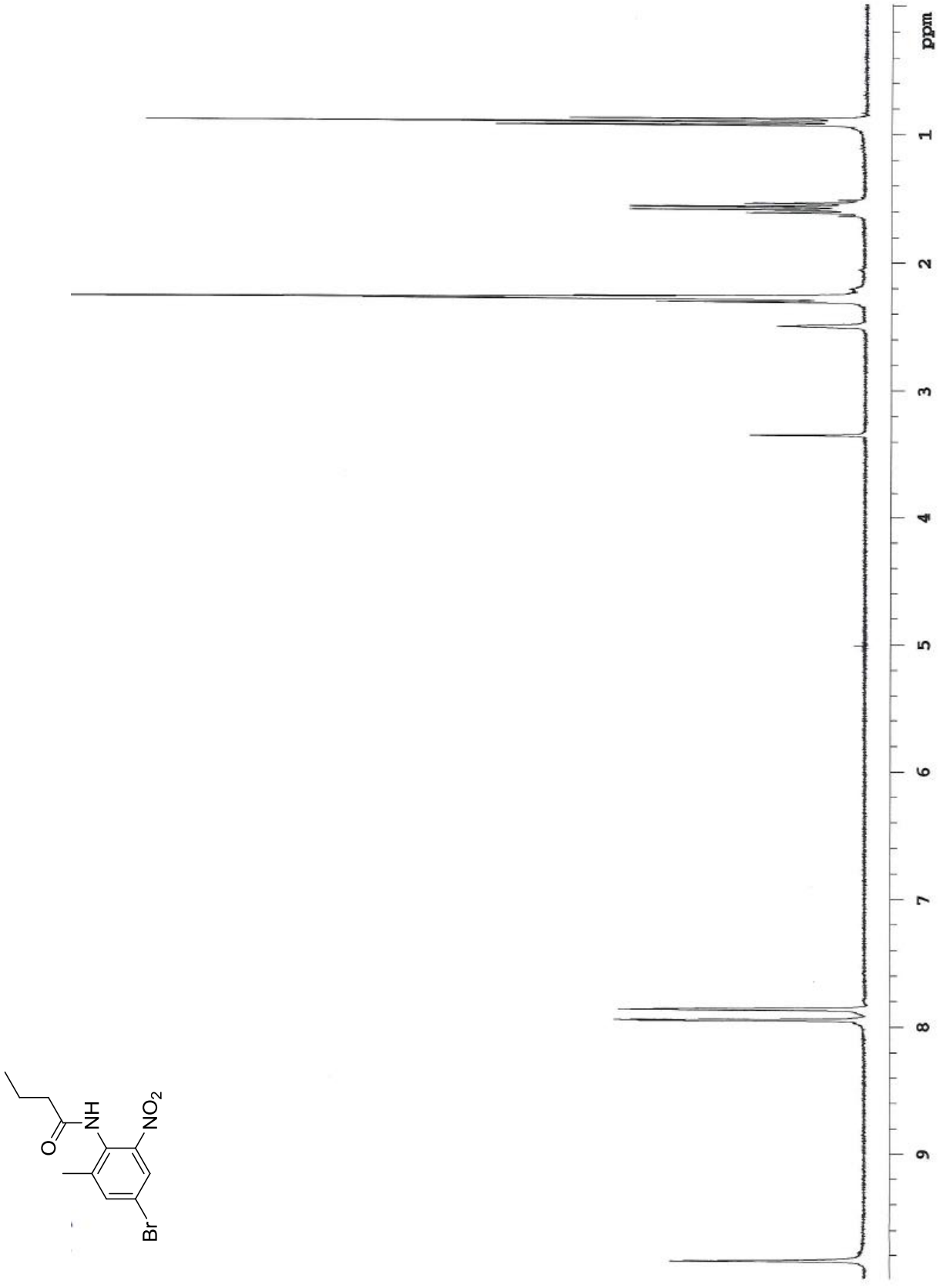




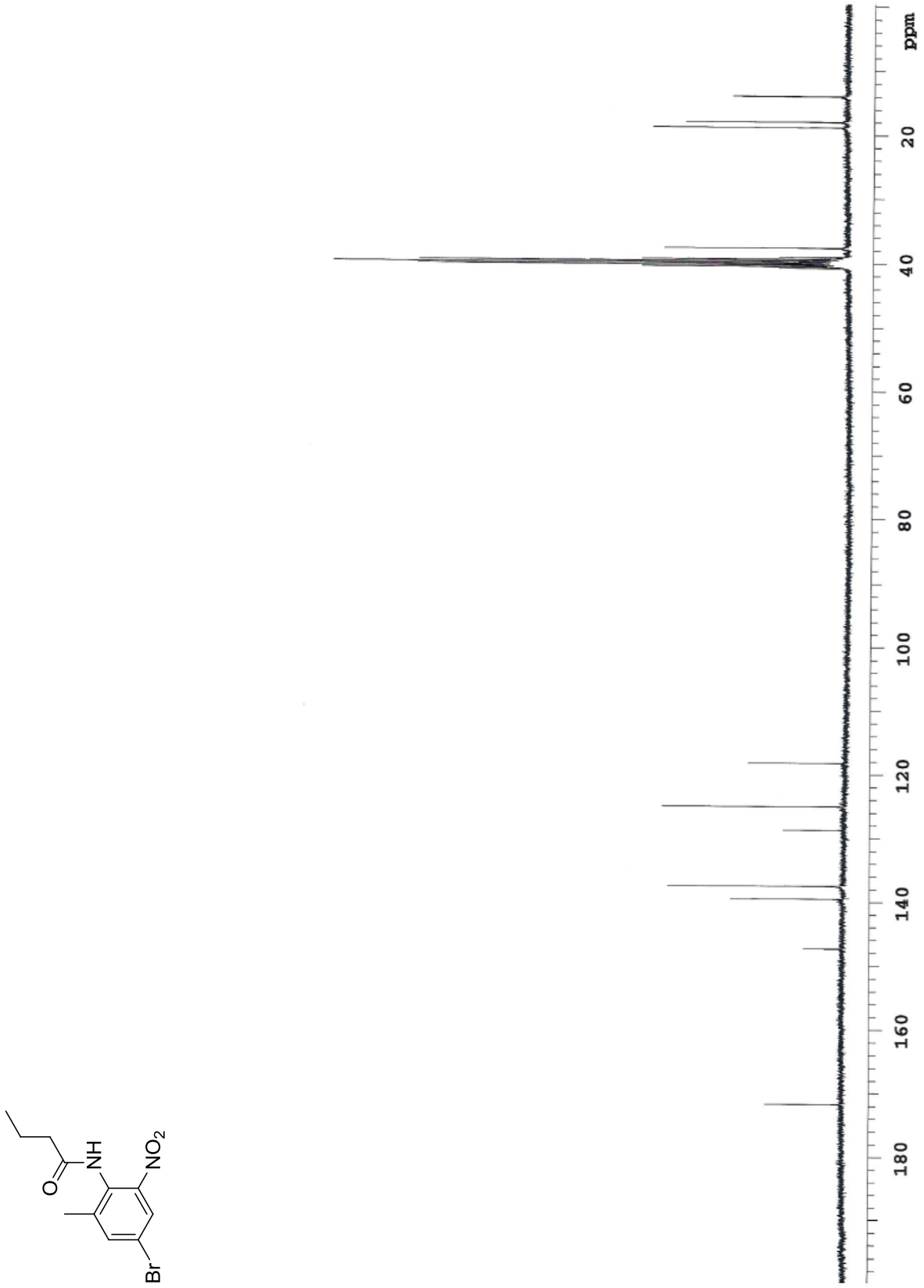
^{13}C NMR: 2-Bromo-1-methylbenzimidazole (54)



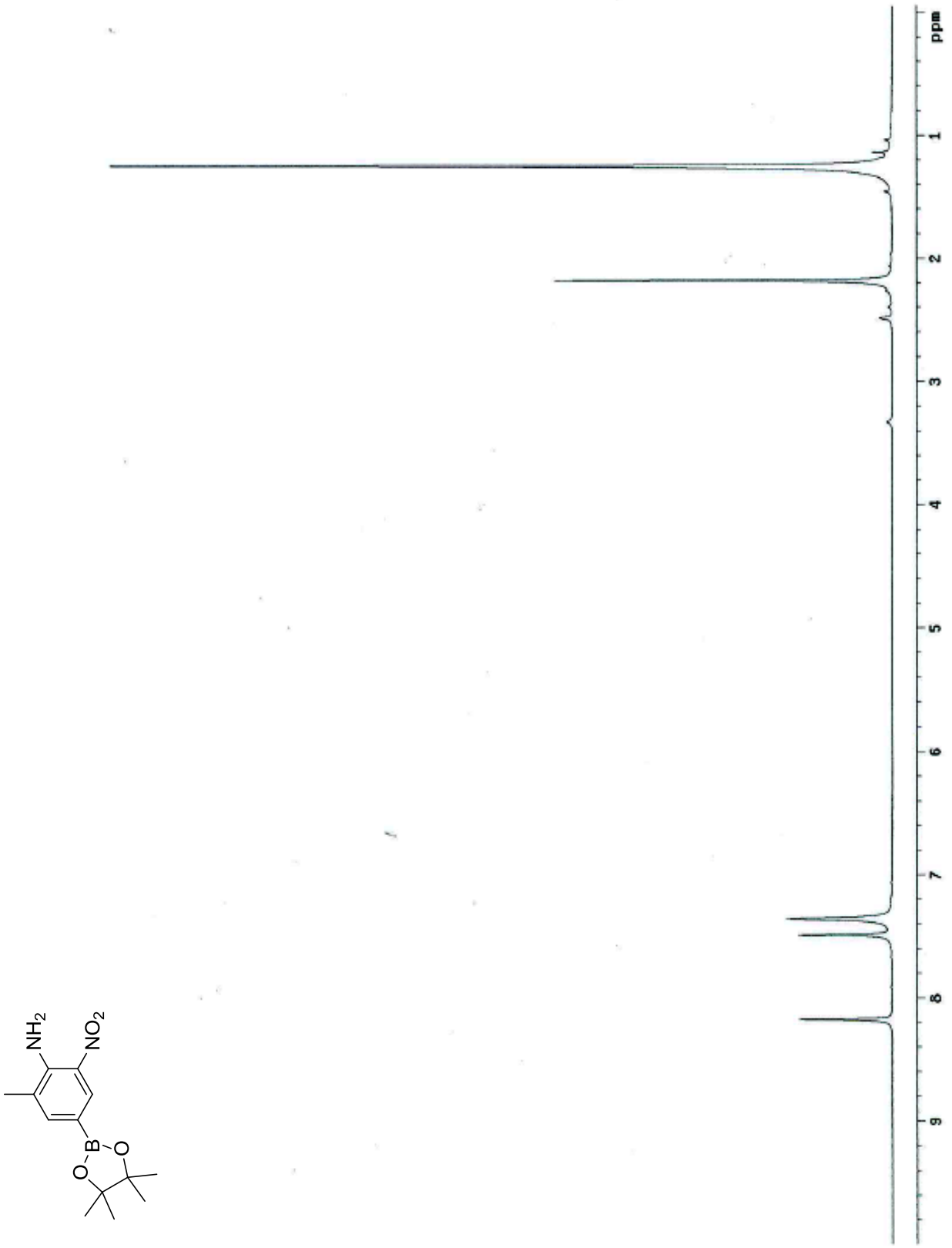
^{1}H NMR: N-(4-Bromo-2-methyl6-nitrophenyl)butyramide (77)



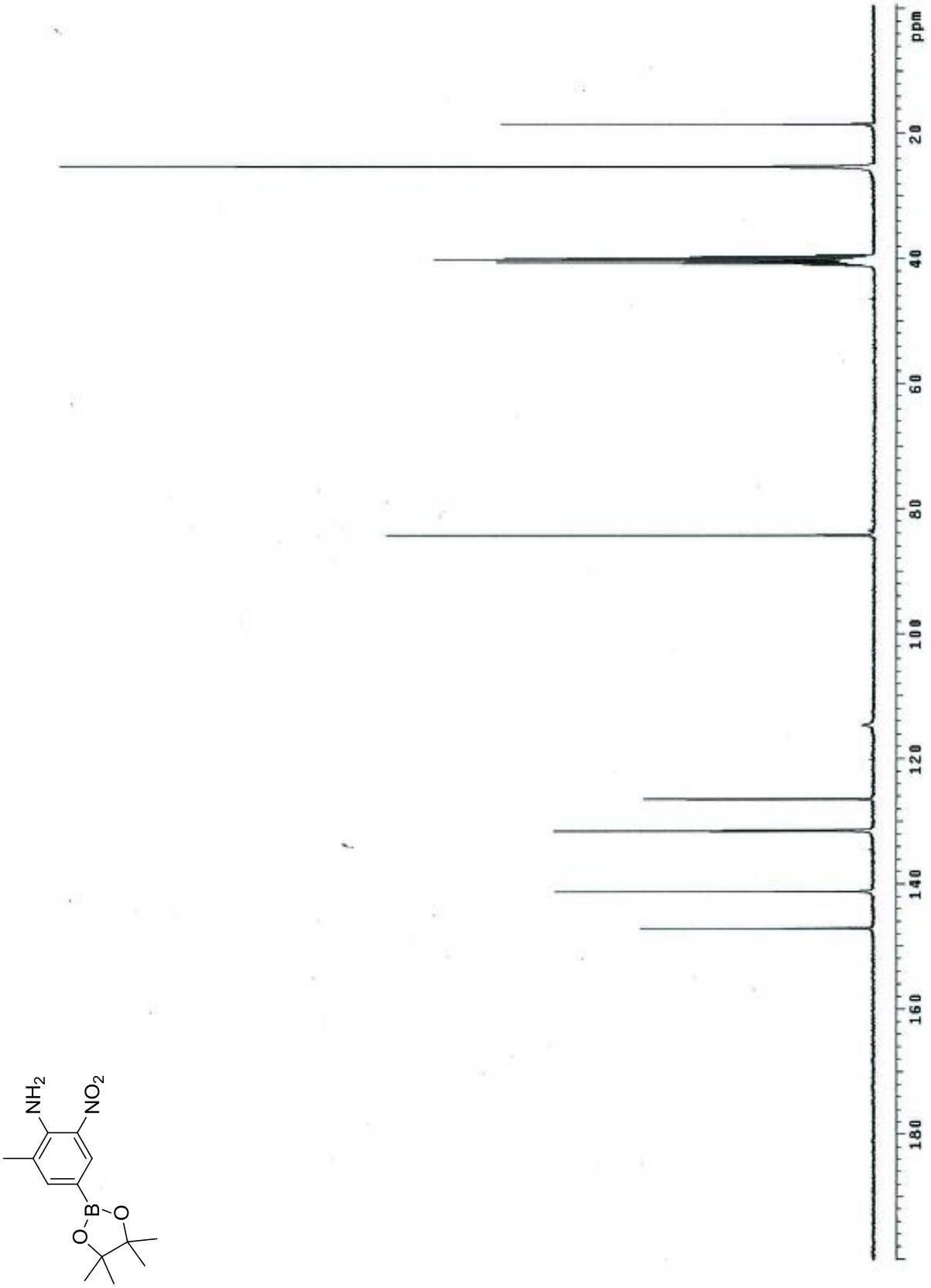
^{13}C NMR: N-(4-Bromo-2-methyl6-nitrophenyl)butyramide (77)



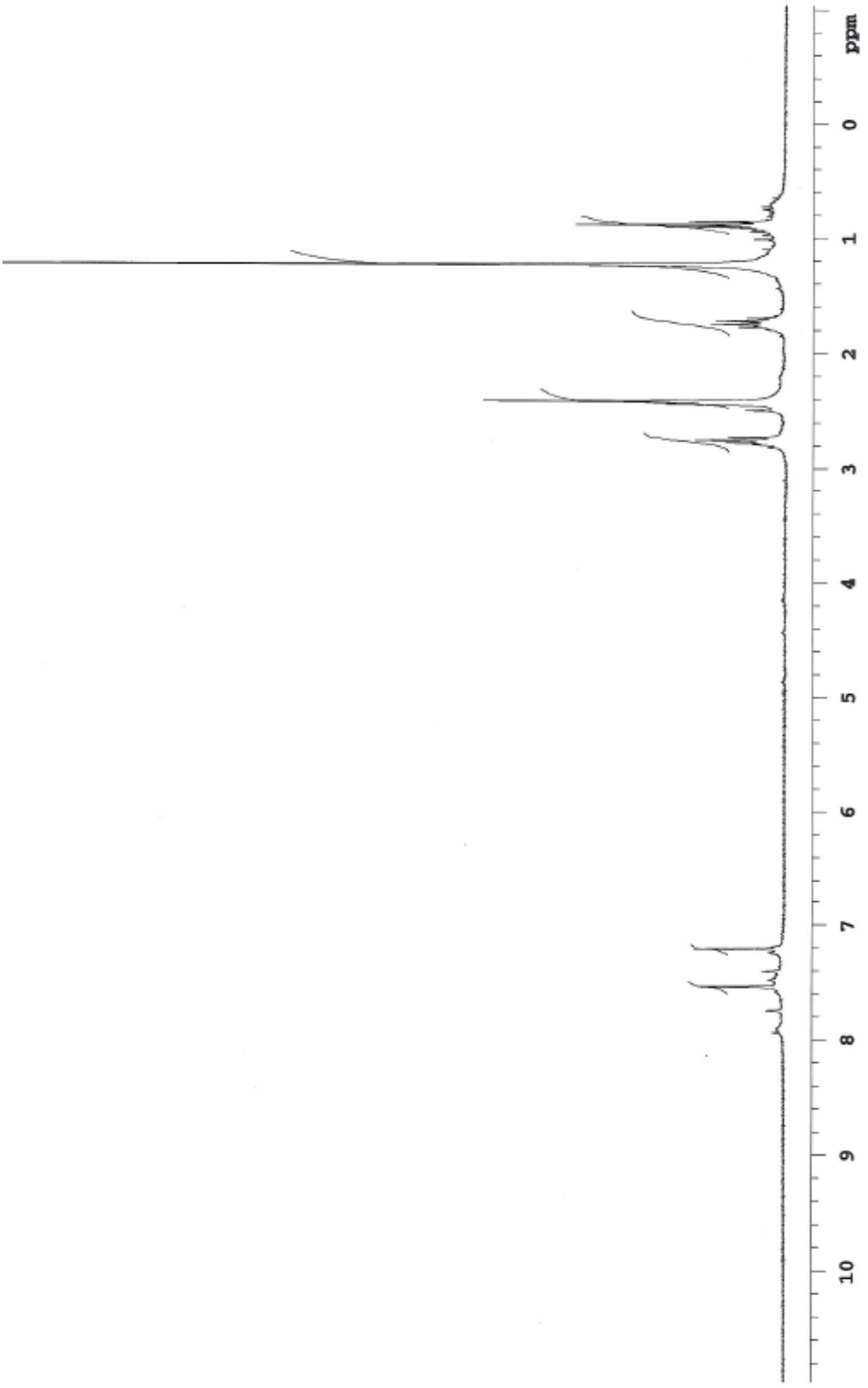
^{1}H NMR: (4-Amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (83)

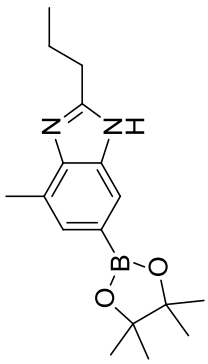


^{13}C NMR: (4-Amino-3-methyl-5-nitrophenyl) boronic acid pinacol ester (83)

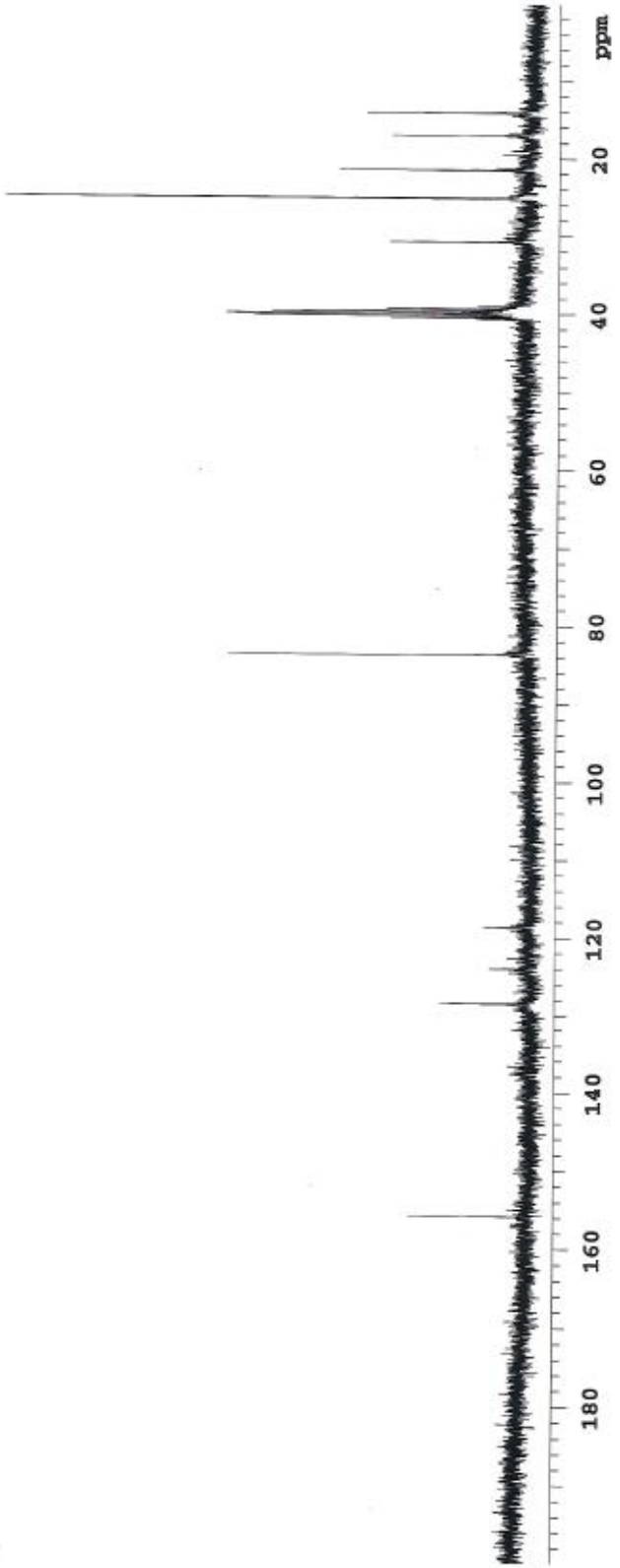


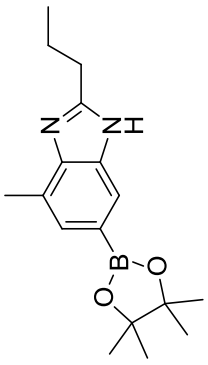
^{1}H NMR: (4-Methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester (87)



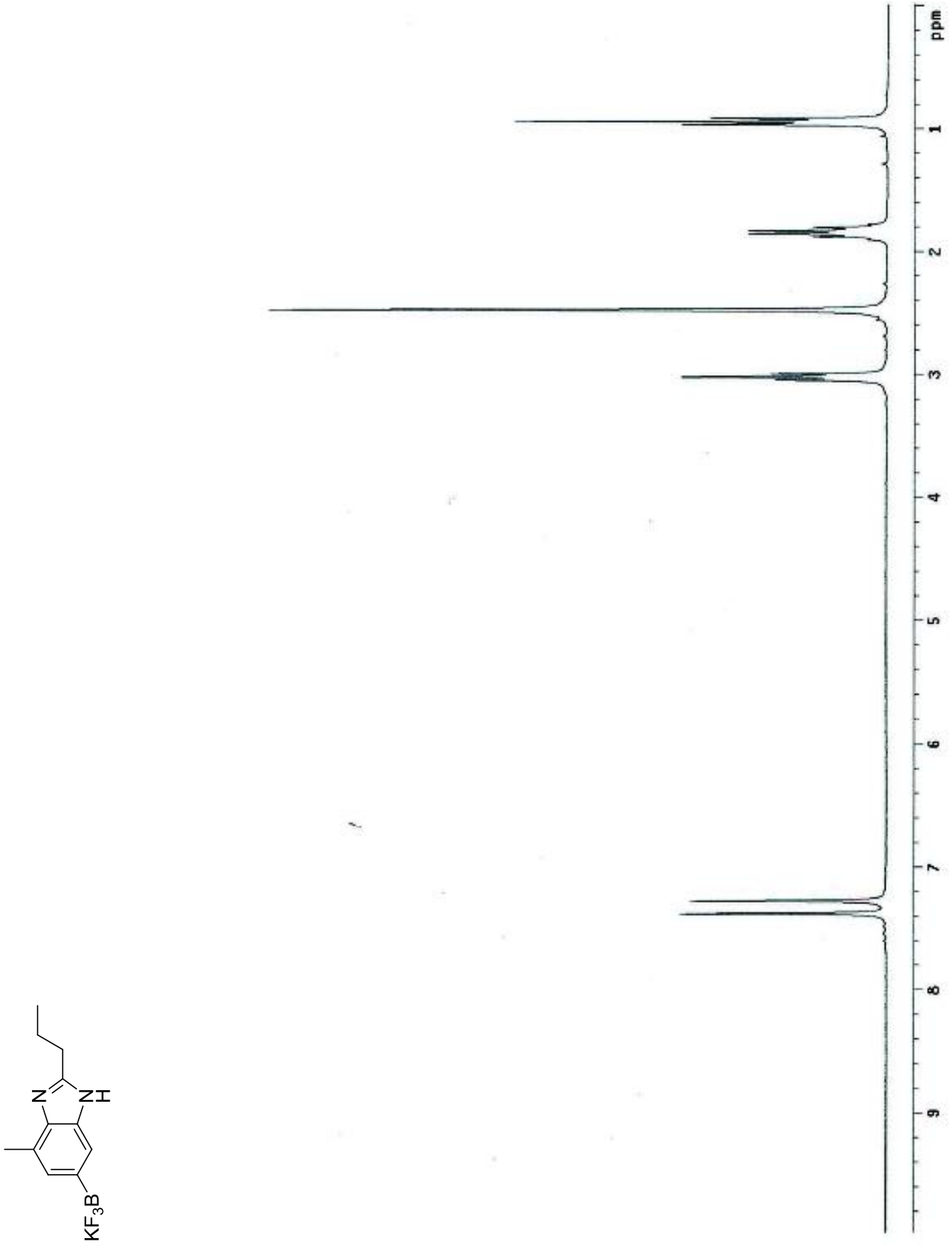


^{13}C NMR: (4-Methyl-2-propylbenzimidazol-6-yl) boronic acid pinacol ester (87)





^{1}H NMR: Potassium (4-methyl-2-propyl-benzimidazol-6-yl) trifluoroborate (65)



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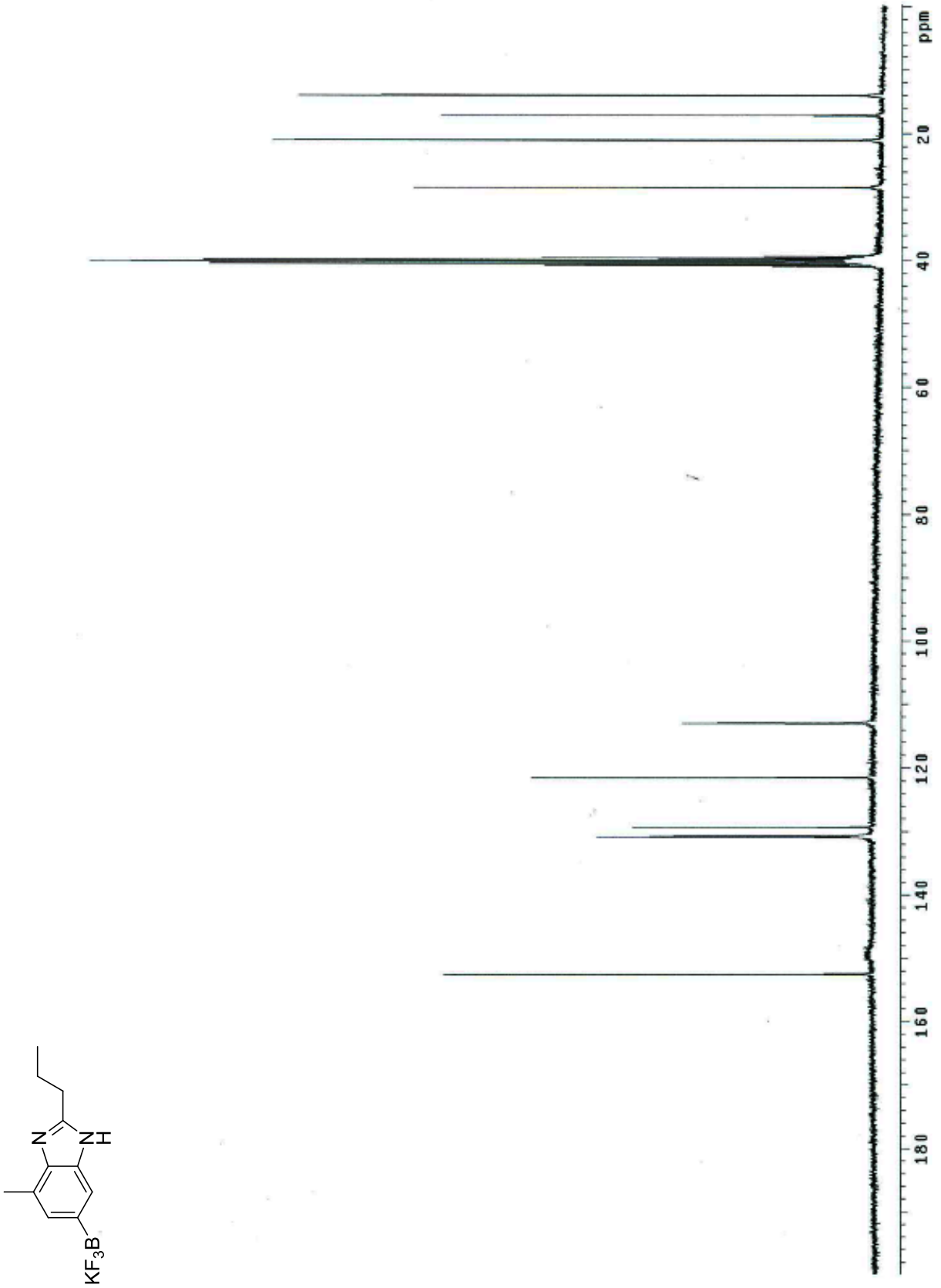
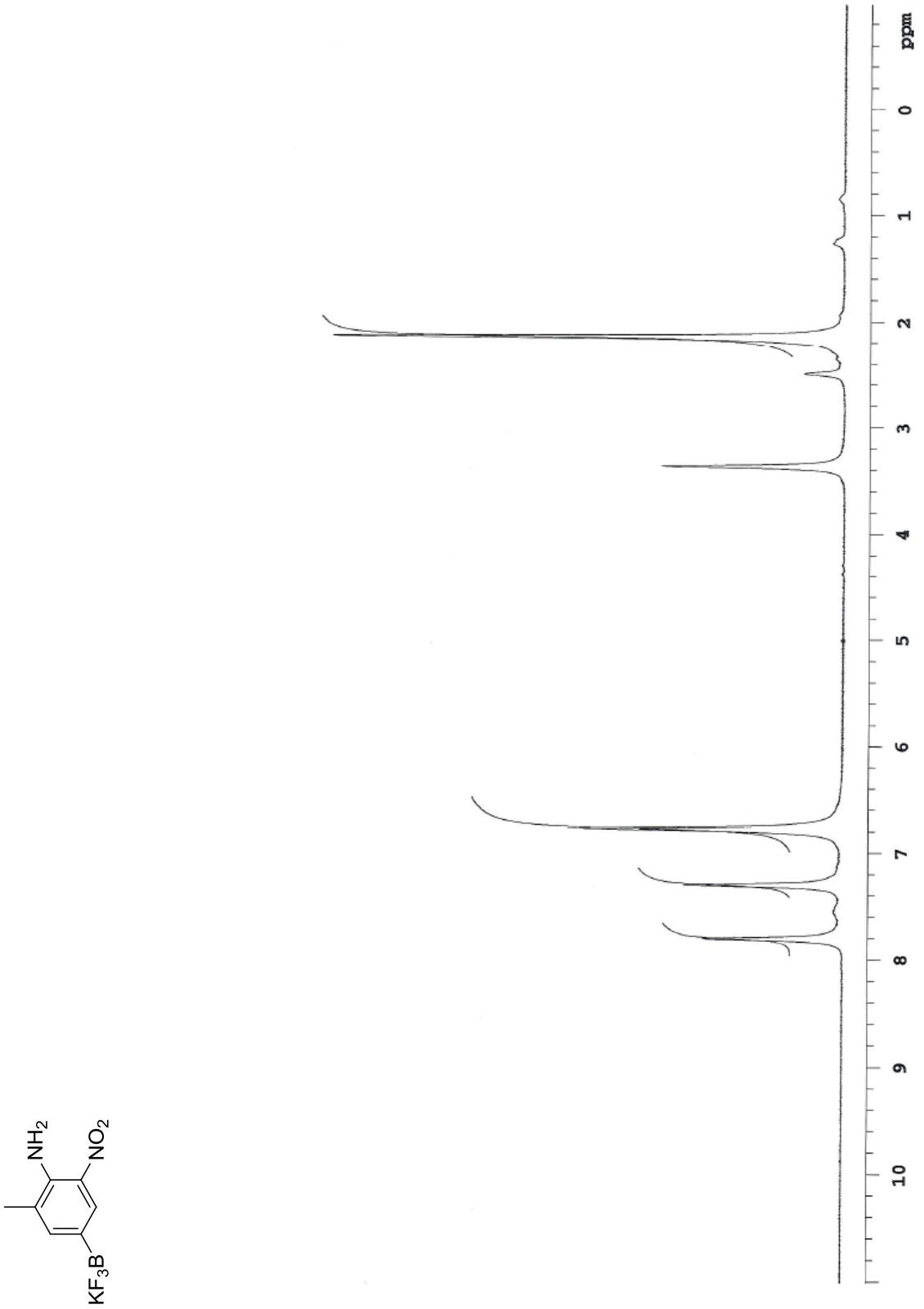
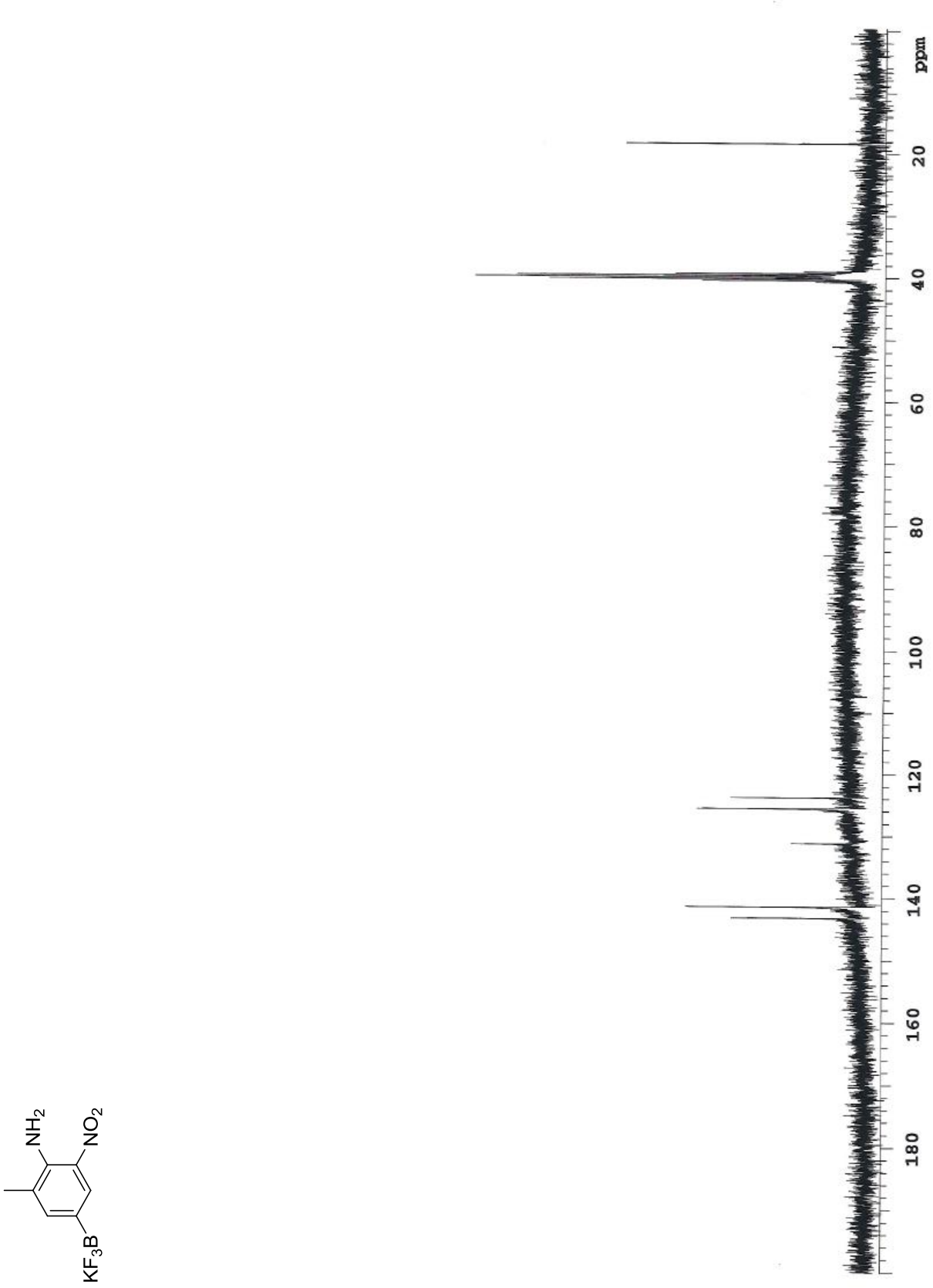


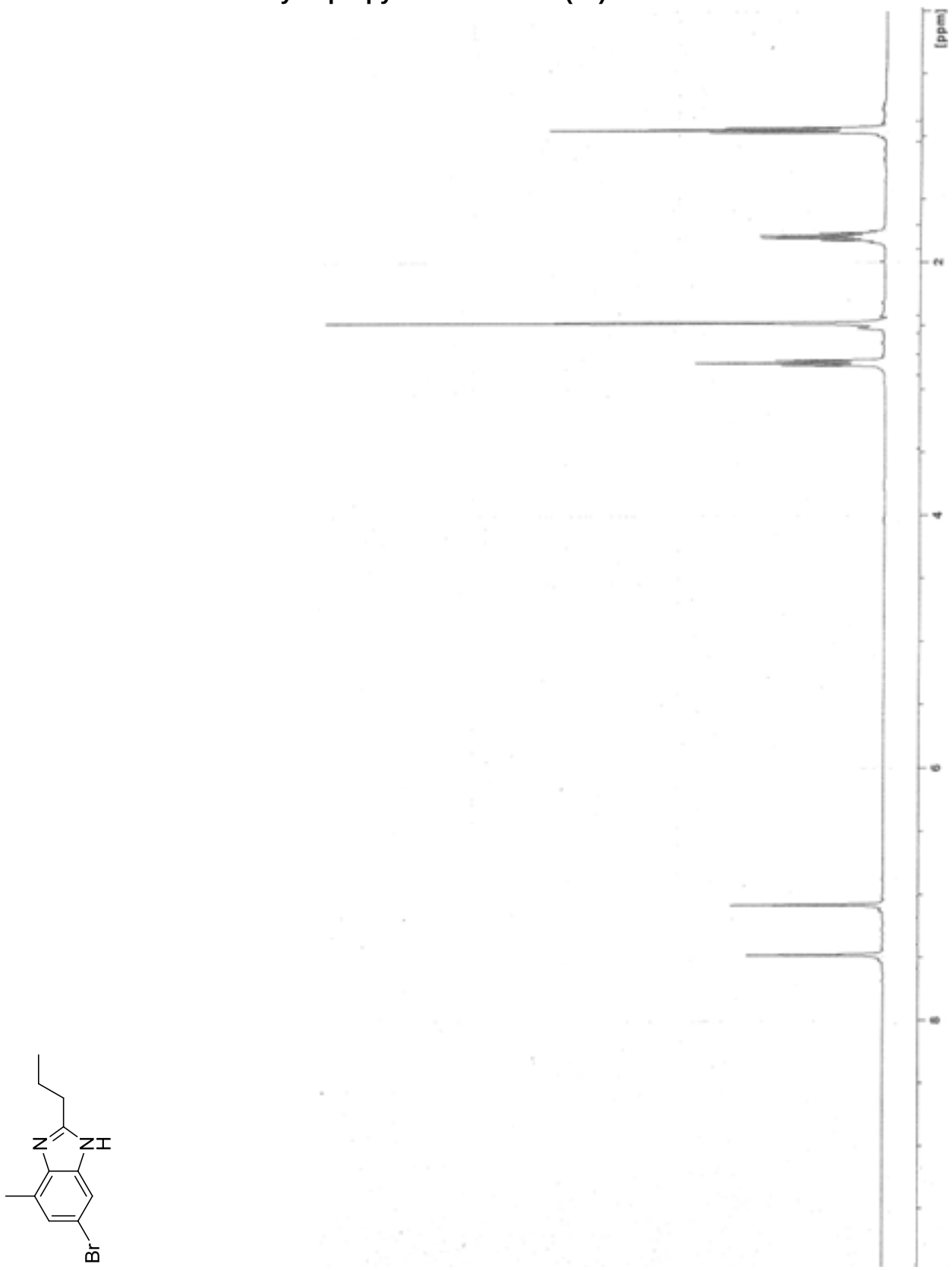
^{1}H NMR: Potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate (88)



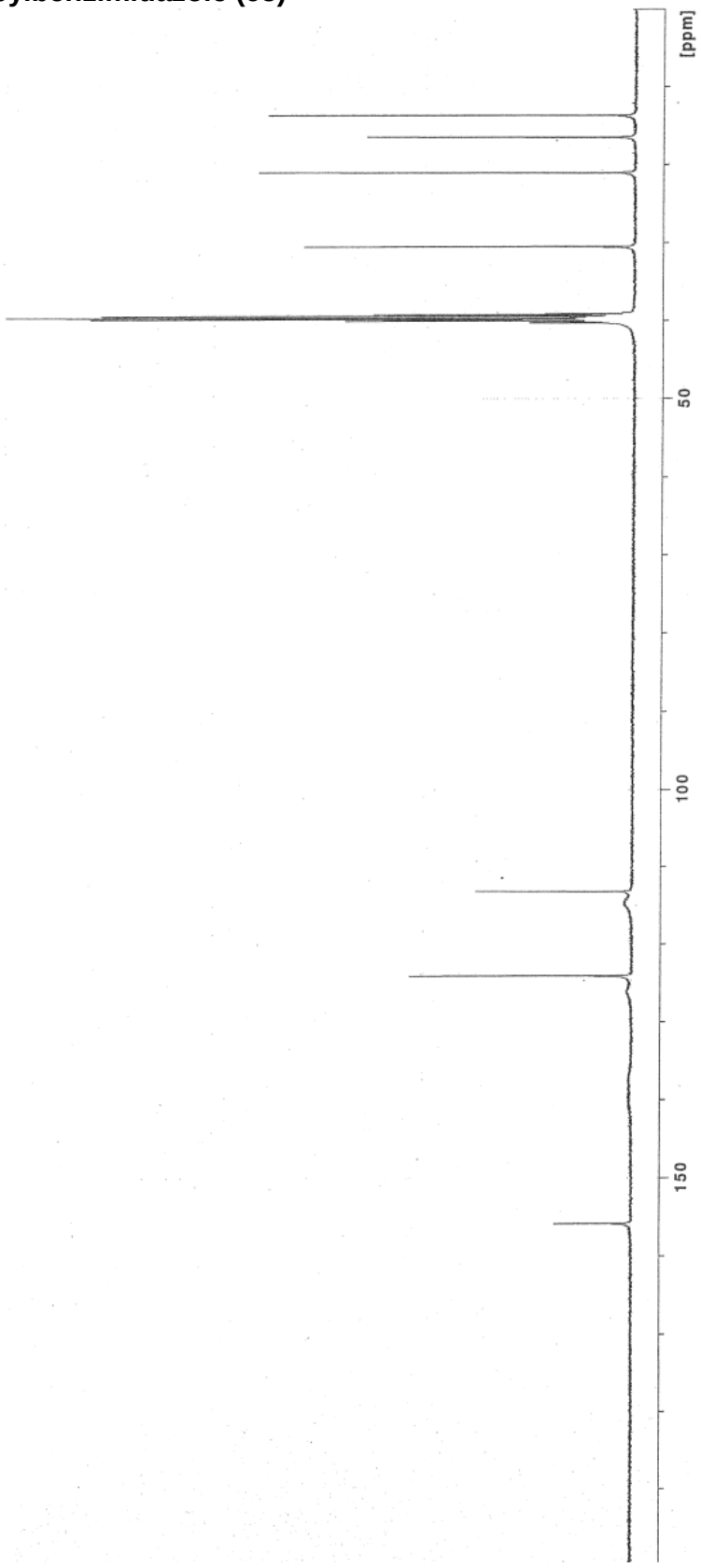
^{13}C NMR: Potassium (4-amino-3-methyl-5-nitrophenyl) trifluoroborate (88)

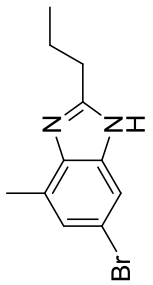


^{1}H NMR: 6-Bromo-4-methyl-2-propylbenzimidazole (95)

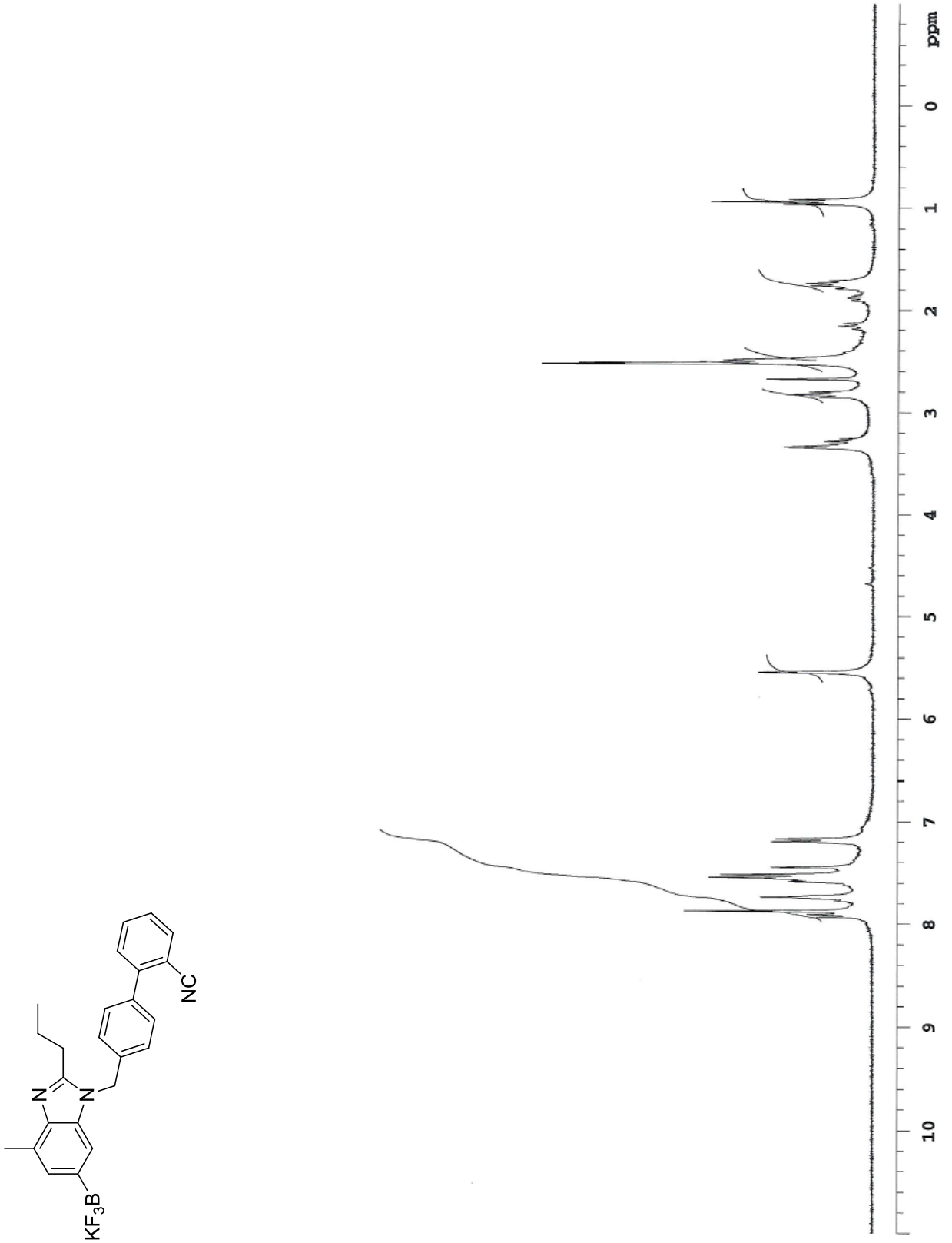


^{13}C NMR: 6-Bromo-4-methyl-2-propylbenzimidazole (95)

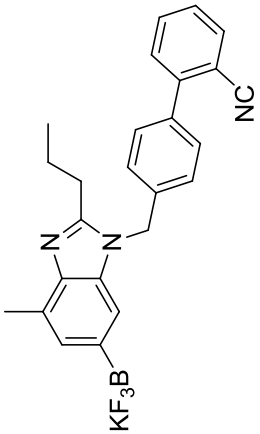


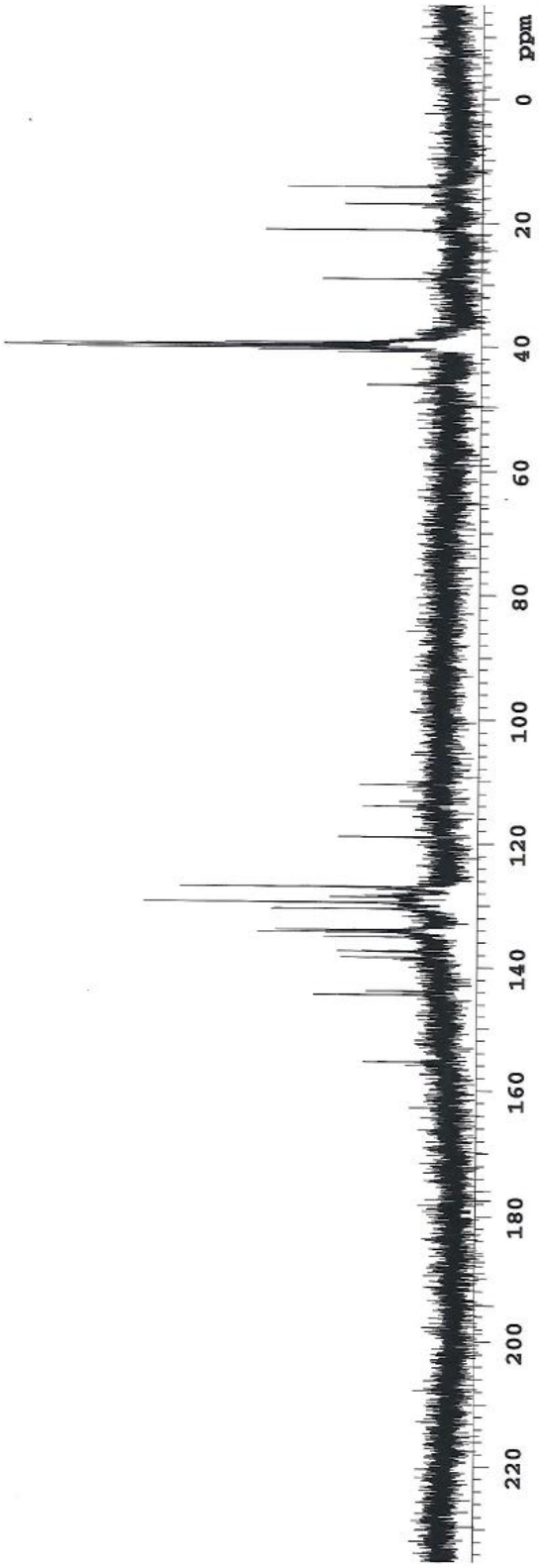


^{1}H NMR: Potassium (1-((2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propylbenzimidazol -6-yl) trifluoroborate (115)

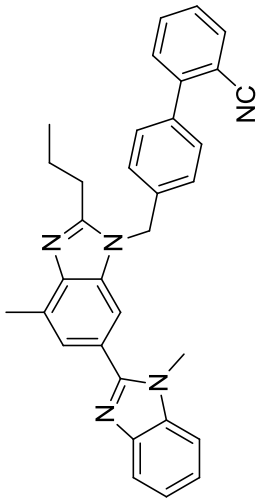


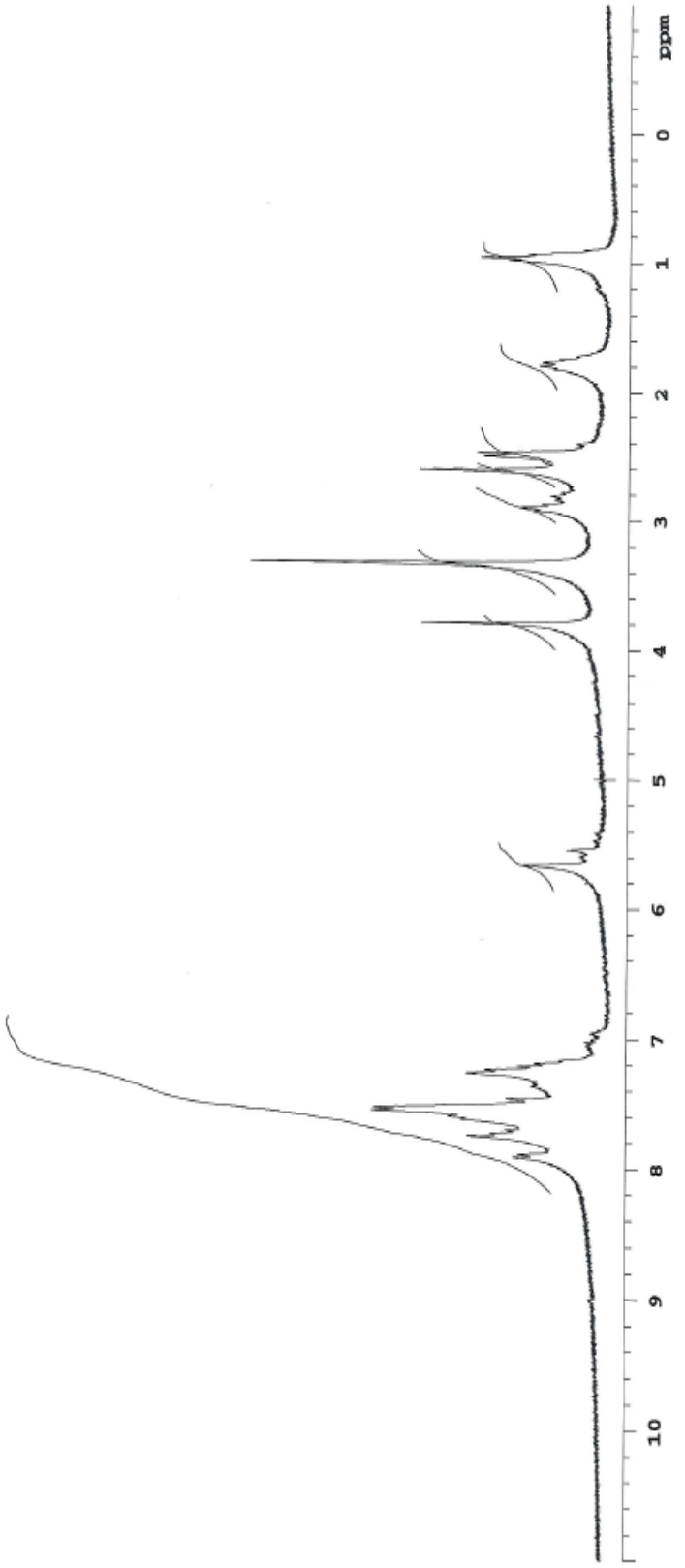
^{13}C NMR: Potassium (1-((2'-cyano-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-2-propylbenzimidazol -6-yl) trifluoroborate (115)



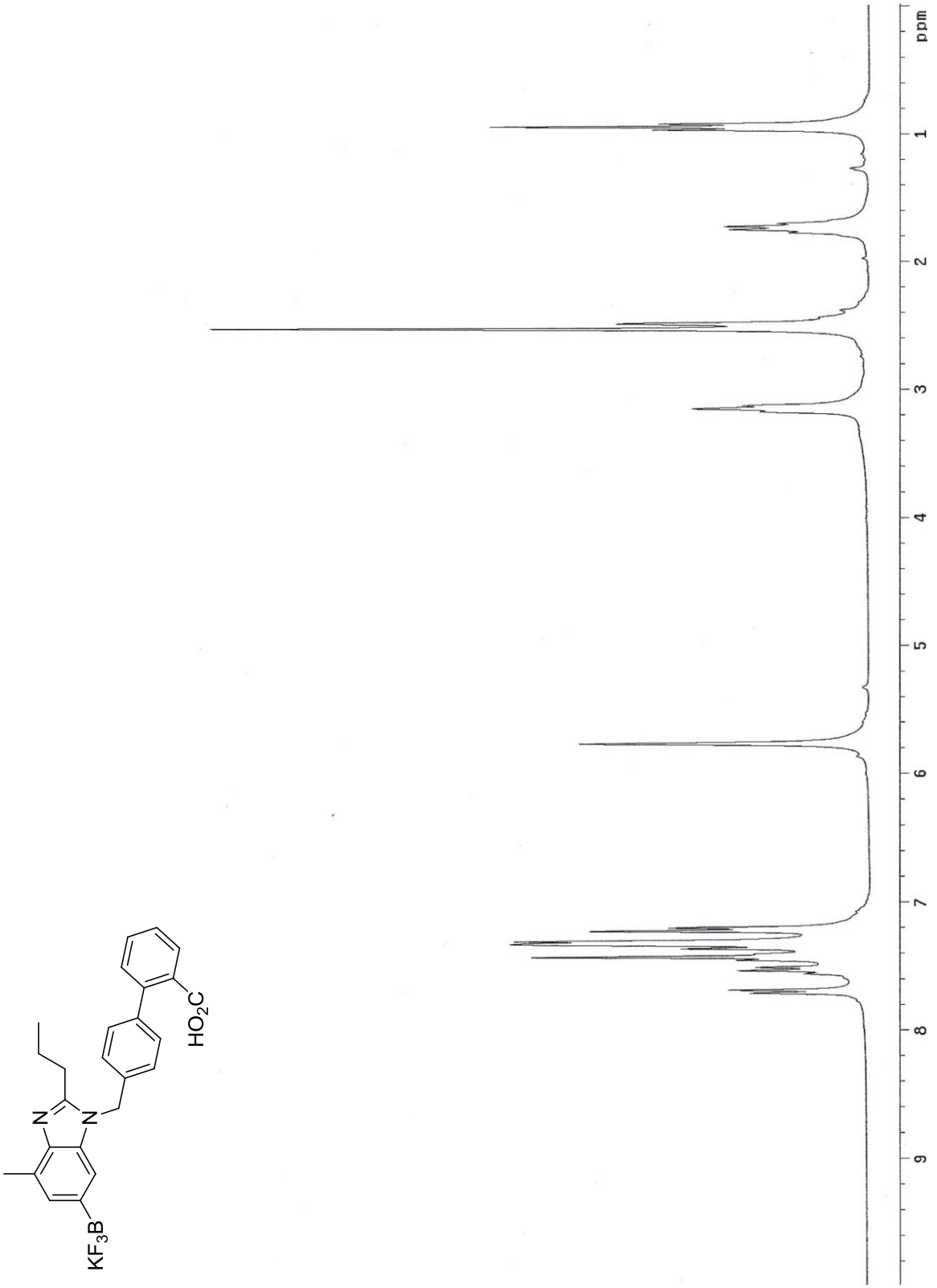


^{1}H NMR: 4'-((1,7'-Dimethyl-2'-propyl-[2,5'-dibenzimidazol]-1'-yl) methyl)-[1,1'-biphenyl]-2-carbo-nitrile (46)





^{1}H NMR: Potassium(1-(2'-carboxy-[1,1'-biphenyl]-4-yl)-4-methyl-2-propyl-benzimidazole-6-yl) trifluoroborate (117)



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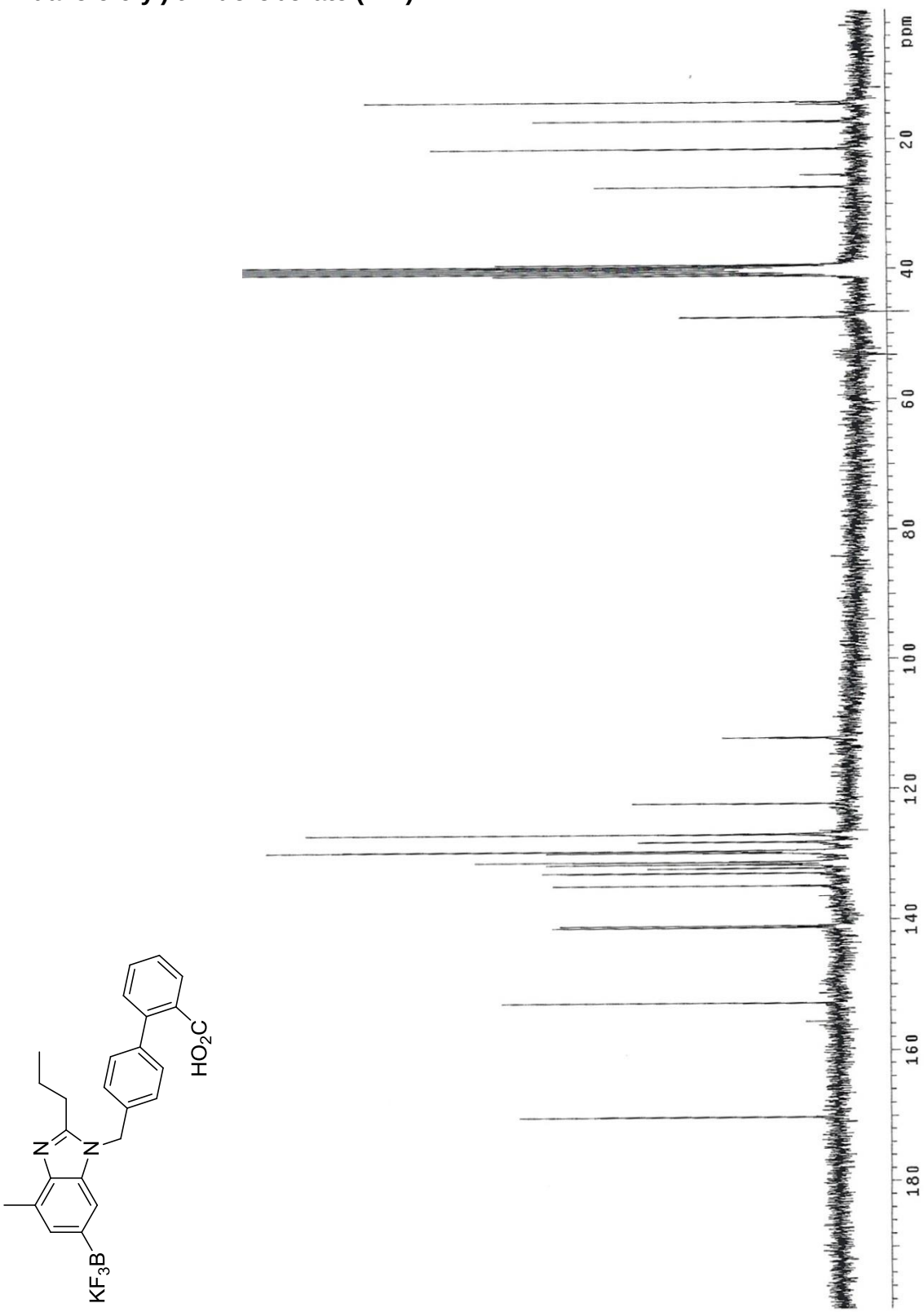
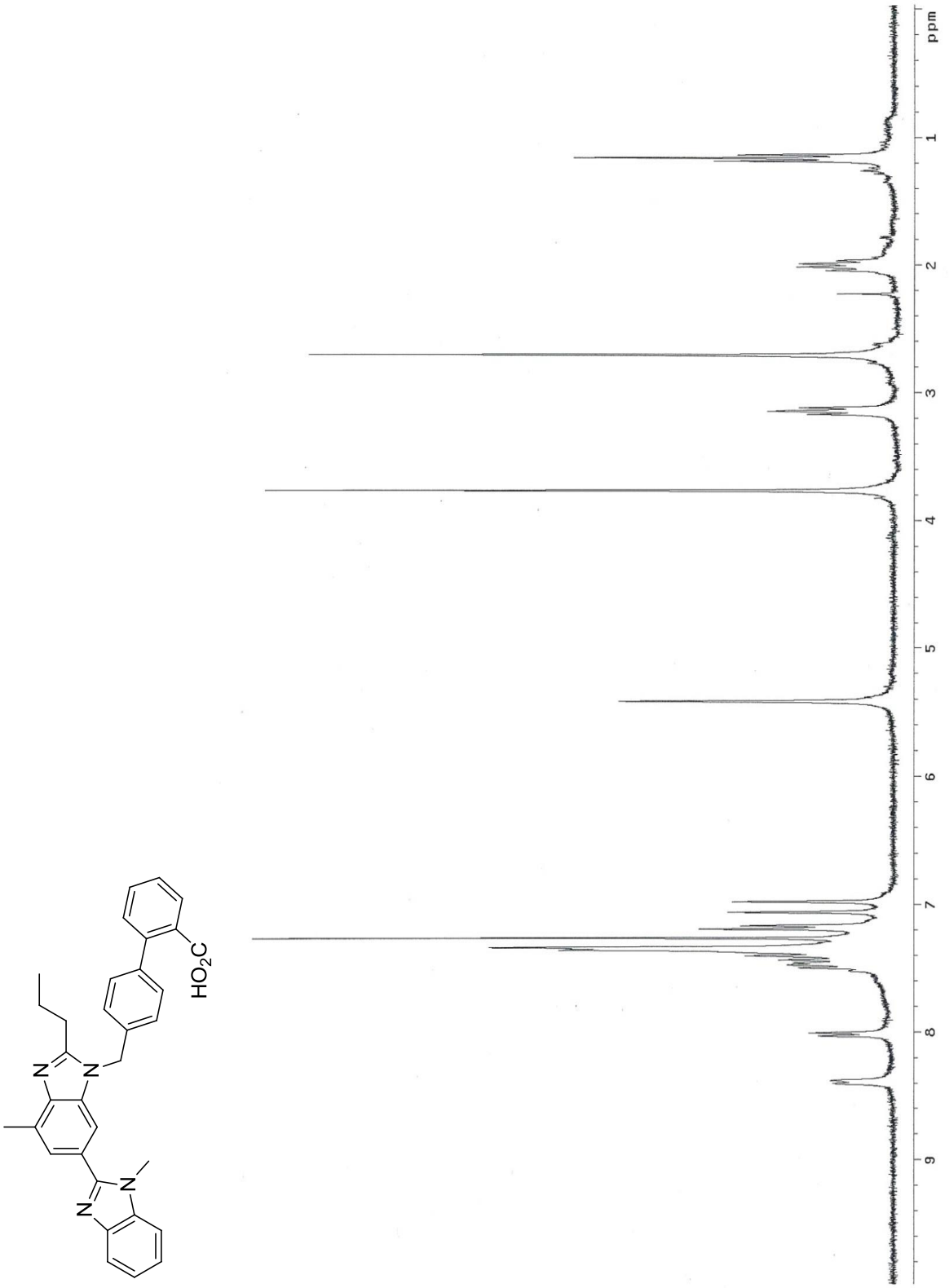
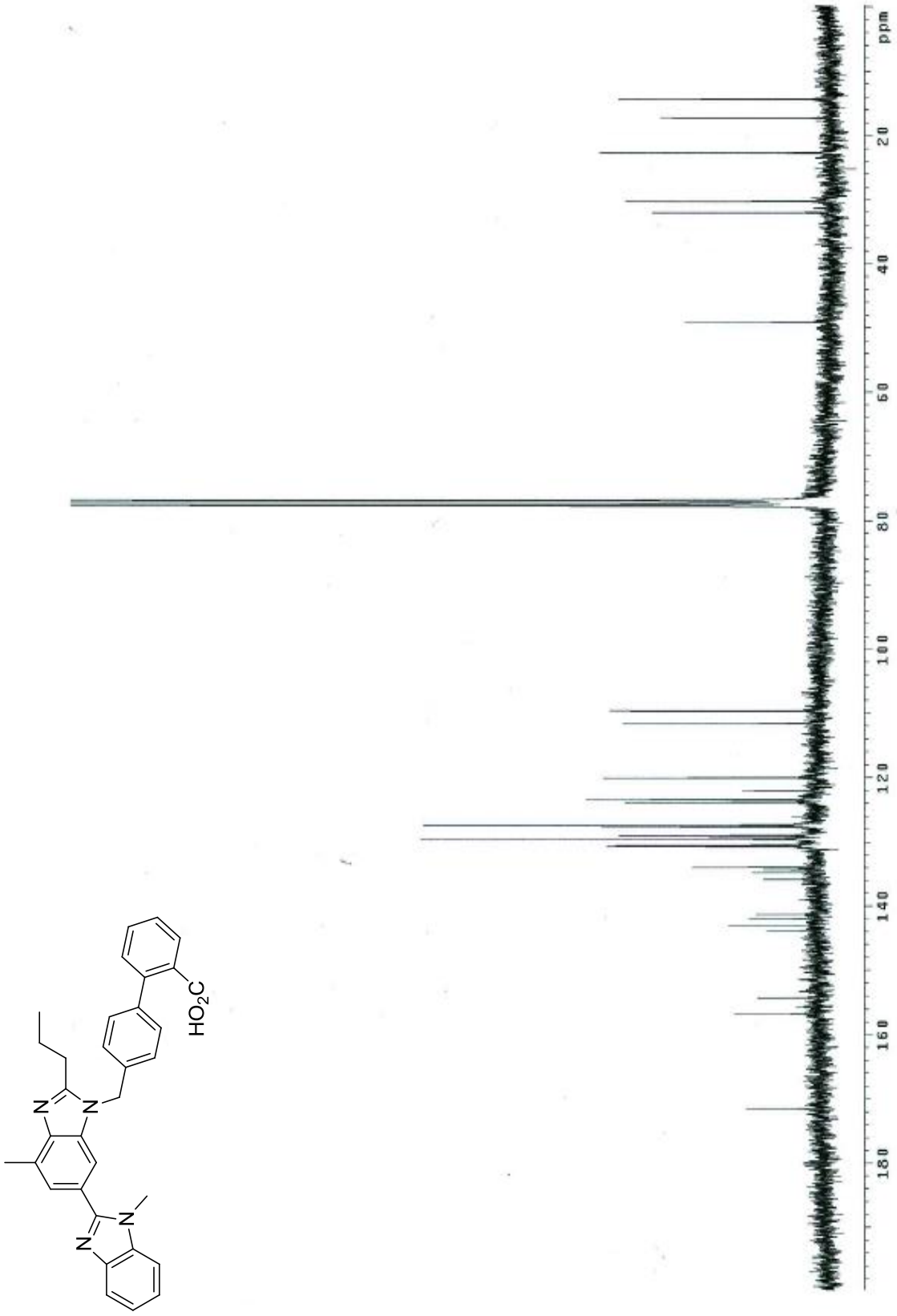


^{1}H NMR: Telmisartan (1)



^{13}C NMR: Telmisartan (1)



VITA

Alex D. Martin was born on May 11, 1987 in Flint, Michigan. In 2009 he received his B.S. Chem Degree from the University of Michigan. He currently lives in Charlottesville, Virginia. He entered the Virginia Commonwealth University doctoral program in 2009.

Publications

1. A.D. Martin, A.R. Siamaki, K. Belecki, B.F. Gupton. “A Convergent Approach to the Total Synthesis of Telmisartan via a Suzuki-Cross Coupling Reaction between Two Functionalized Benzimidazoles.” *J Org Chem*. **2015**. 80 (3), 1915-1919.
2. A.D. Martin, A.R. Siamaki, K. Belecki, B.F. Gupton. “A Flow-based Synthesis of Telmisartan.” *J Flow Chem*. **2015**. (in press, DOI:10.1556/JFC-D-15-00002)
3. J. Pannu, A. McCarthy, A. Martin, T. Hamouda, S. Ciotti, L. Ma, J. Sutcliffe, J.R. Baker. “*In Vitro* Antibacterial Activity of NB-003 against *Propionibacterium acnes*.” *Antimicrob Agents Chemother*. **2011**. 55, 4211-4217.
4. J. Pannu, A. McCarthy, A. Martin, T. Hamouda, S. Ciotti, A. Fothergill, J. Sutcliffe. “NB-002, A Novel Nanoemulsion with Broad Antifungal Activity against Dermatophytes, Other Filamentous Fungi and *Candida albicans*.” *Antimicrob Agents Chemother*. **2009**. 53 (8), 3273-3279.
5. X. Lu, J. Han, N. Shepherd, A. Martin, D. Li, G. Xue, Z. Chen. “Phenolic Resin Surface Restructuring upon Exposure to Humid Air: A Sum Frequency Generational Vibrational Spectroscopy Study.” *J Phys Chem B*. **2009**. 113 (39), 12944-12951.

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